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54

IN THIS ISSUE

- Randomized clinical trial of laparoscopic *versus* open abdominal rectopexy for rectal prolapse
- Randomized clinical trial comparing the efficacy of two bandaging regimens in the treatment of venous leg ulcers
- Randomized trial of Lichtenstein *versus* Shouldice hernia repair in general surgical practice
- Randomized clinical trial of suture repair, polypropylene mesh or autodermal hernioplasty for incisional hernia

THIS MONTH ON THE WEBSITE

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- Evidence-based surgery
- Minimally invasive surgery
- The surgeon as a risk factor
- Teaming up with gastroenterologists
- Multi-disciplinary approach to cancer
- GI oncology - from DNA to patient
- Living-related liver transplant
- Psychosocial oncology

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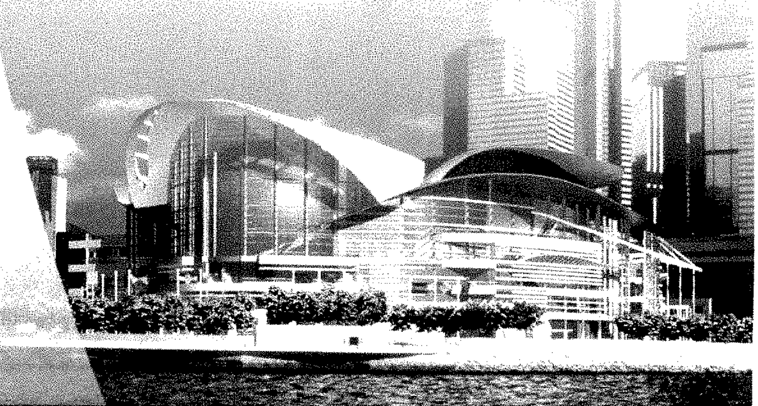

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Contents

British Journal of Surgery

Volume 89, Issue 1, January 2002

Leading articles

1 **Virtual colonoscopy**
H. M. Fenlon
A potential cancer screening tool

4 **Aspirin resistance**
J. Smout and G. Stansby
Aspirin does not always achieve the desired antiplatelet effect

Consensus statement

6 **Consensus statement on submission and publication of manuscripts**
Surgical Journal Editors Group
More guidance on duplicate and fraudulent publication

Reviews

8 **Restriction enzymes in the analysis of genetic alterations responsible for cancer progression**
G. J. S. Jenkins, G. L. Williams, J. Beynon, Z. Ye, J. N. Baxter and J. M. Parry
Over 200 restriction enzymes are currently available and more will be created

21 **Sentinel lymph node biopsy and breast cancer**
M. Noguchi
The elimination of routine axillary lymph node dissection is considered

Randomized trials

35 **Randomized clinical trial of laparoscopic *versus* open abdominal rectopexy for rectal prolapse**
M. J. Solomon, C. J. Young, A. A. Eyers and R. A. Roberts
Laparoscopic technique better

40 **Randomized clinical trial comparing the efficacy of two bandaging regimens in the treatment of venous leg ulcers**
F. J. Meyer, K. G. Burnand, N. R. F. Lagattolla and D. Eastham
No advantage for increasing compression

45 **Randomized trial of Lichtenstein *versus* Shouldice hernia repair in general surgical practice**
P. Nordin, P. Bartelmess, C. Jansson, C. Svensson and G. Edlund
Fewer recurrences after Lichtenstein repair

50 **Randomized clinical trial of suture repair, polypropylene mesh or autodermal hernioplasty for incisional hernia**
M. Korenkov, S. Sauerland, M. Arndt, L. Bograd, E. A. M. Neugebauer and H. Troidl
The trial was stopped due to mesh infections

Original articles

57 **Liver fibrosis increases the risk of intrahepatic recurrence after hepatectomy for hepatocellular carcinoma**
S. Ko, H. Kanehiro, M. Hisanaga, M. Nagao, N. Ikeda and Y. Nakajima
A histological review of 138 operations

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63 **Preoperative hepatic venous embolization for partial hepatectomy combined with segmental resection of major hepatic vein**
Y. Ku, M. Tominaga, T. Sugimoto, T. Iwasaki, T. Fukumoto, T. Takahashi, Y. Suzuki and Y. Kuroda
May avoid hepatic vein reconstruction

70 **Effect of chronic renal failure on mortality rate following arterial reconstruction**
D. J. Gerrard, S. A. Ray, E. A. Barrio, C. H. Wood, J. E. Scoble and P. R. Taylor
Mortality rate was three times greater

74 **Value of isotope lymphography in the diagnosis of lymphoedema of the leg**
K. G. Burnand, C. L. McGuinness, N. R. F. Lagattolla, N. L. Browse, A. El-Aradi and T. Nunan
First line investigation for lymphoedema

79 **Fissurectomy and isosorbide dinitrate for chronic fissure *in ano* not responding to conservative treatment**
A. F. Engel, Q. A. J. Eijsbout and A. G. Balk
Useful treatment for chronic fissure

84 **Optimum number of core biopsies for accurate assessment of histological grade in breast cancer (short note)**
C. McIlhenny, J. C. Doughty, W. D. George and E. A. Mallon
Four core biopsies should be taken routinely

86 **Detection of micrometastases in lymph nodes from patients with breast cancer**
G. Branagan, D. Hughes, M. Jeffrey, C. Crane-Robinson and P. M. Perry
Investigation of mammaglobin expression improves staging

90 **Prospective study of open preperitoneal mesh repair for recurrent inguinal hernia**
M. Kurzer, P. A. Belsham and A. E. Kark
Results superior to conventional anterior approach

94 **Prediction of serious complications in patients admitted to a surgical ward**
S. C. Veltkamp, J. M. Kemmeren, Y. van der Graaf, M. Edlinger and C. van der Werken
Useful model to predict patients at risk

103 **Time course of peritoneal tissue plasminogen activator after experimental colonic surgery: effect of hyaluronan-based antiadhesive agents and bacterial peritonitis**
M. M. P. J. Reijnen, L. Holmdahl, T. Kooistra, P. Falk, T. Hendriks and H. van Goor
An experimental study that has implications for adhesion formation

110 **Risk-adjusted surgical audit with the POSSUM scoring system in a developing country**
M. K. Yii and K. J. Ng
Portsmouth POSSUM is universally applicable

b
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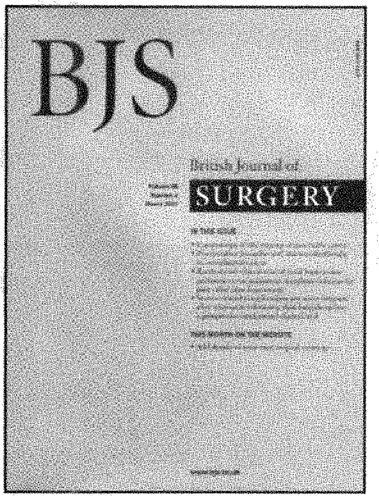

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114 **One visual analogue pain score is sufficient after laparoscopic cholecystectomy (short note)**
W. Schwenk, J. W. Mall, J. Neudecker and J. M. Müller
Only one pain score is necessary

116 **Botulinum toxin A in the treatment of patients with Frey syndrome**
A. J. F. Beerens and G. B. Snow
Repeat treatment increases the effectiveness

120 **Corrigendum**

122 **Correspondence**

124 **Book reviews**

126 **Scientific surgery**

127 **Instructions to authors**

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Virtual colonoscopy

H. M. Fenlon

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Virtual colonoscopy is a powerful new method of imaging the colon. It involves thin-section helical computed tomography (CT) of the clean, air-distended colon, with images viewed in a variety of two- and three-dimensional formats (*Figs 1* and *2*). Since its first description in 1994 the method has been studied extensively and its performance has steadily improved thanks to the development of ultrafast helical CT scanners (multidetector CT) and advances in computer software for image reconstruction[1–4]. The appeal of virtual colonoscopy is that it is a simple, safe and minimally invasive way of evaluating the entire colon, with reported polyp detection rates surpassing those published for double-contrast barium enema and approaching those of conventional colonoscopy.

Although a variety of techniques has been described, the same basic principles apply to all: full bowel cleansing, air distension of the colon using a rectal enema tube, acquisition of both supine and prone thin-section images of the colon, and image interpretation using a combination of axial and multiplanar or endoluminal reconstructions. Optimizing patient preparation is an important consideration when performing virtual colonoscopy as both retained

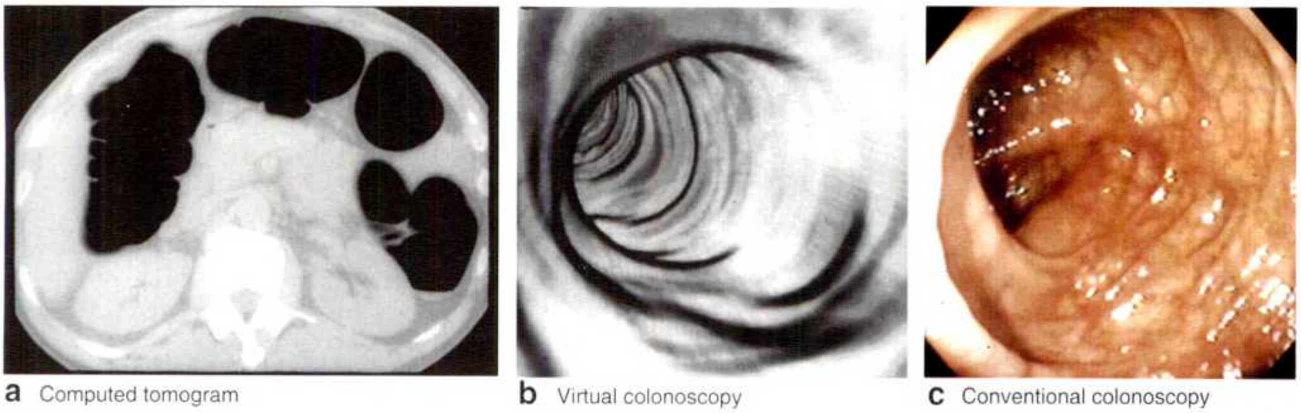

Fig. 1 **a** Axial computed tomogram demonstrating a normal, clean and well distended colon. **b** Endoluminal view at virtual colonoscopy of a normal sigmoid colon. **c** Same segment of normal colon as in **b**, seen at conventional colonoscopy

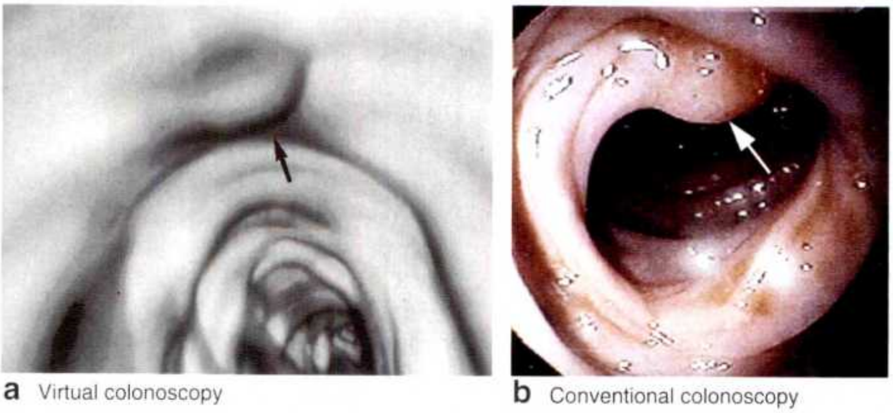

Fig. 2 **a** Virtual colonoscopy image demonstrating a 12-mm polyp (arrow) in the transverse colon. **b** Same polyp (arrow) as in **a**, seen at conventional colonoscopy

intraluminal fluid and stool may mimic or disguise colonic pathology. Currently, full bowel cleansing using either a phosphosoda (Fleet®, E. C. De Witt and Co., Runcorn, UK) or a polyethylene glycol (Klean-Prep®, Helsin Birex, Dublin, Ireland) preparation is required; phosphosoda preparations are preferred as they result in a drier mucosal surface[3]. All investigators now agree on the need for maximal air distension of the colon and routine acquisition of both supine and prone scans to help overcome problems with collapsed segments of colon and to differentiate residual stool from pathology. The routine use of spasmolytics (glucagon or hyoscine butylbromide) has been abandoned because they have not been shown to improve colonic distension, patient comfort or test accuracy[5]. For the patient, a complete virtual colonoscopy examination should require no more than 10–15 min in the scanning department. For the radiologist, although a substantial learning curve exists, a full virtual colonoscopy examination can be reviewed using axial two-dimensional images and limited three-dimensional reconstructions in as little as 10 min.

Published results indicate that the sensitivity of virtual colonoscopy for colorectal cancer exceeds 95 per cent; for polyps measuring 1 cm or more in size it is 80–95 per cent and for those of 6–9 mm it is 65–80 per cent, falling to 35–65 per cent for polyps measuring 5 mm or less[1–5]. Similarly encouraging data exist for specificity for polyps and cancer, with an overall specificity exceeding 87 per cent for lesions of 1 cm or more. Virtual colonoscopy provides a total colonic examination in over 90 per cent of patients, even in those who have distal occlusive colorectal cancer that cannot be passed endoscopically, in the frail and the elderly, and in circumstances of failed or incomplete colonoscopy[6,7]. Indeed, both published results and personal experience suggest that virtual colonoscopy should be the investigation of choice in patients following failed colonoscopy, and local clinical practice has changed accordingly.

In theory, virtual colonoscopy has several advantages over existing colorectal cancer screening techniques[8,9]. As a full structural colonic examination, its diagnostic potential should be much greater than faecal occult blood testing and, for the same reason, it should yield substantially more neoplasms than flexible sigmoidoscopy. As a total colonic examination it competes directly with barium enema and colonoscopy. To date, all studies have involved direct comparisons of virtual and conventional colonoscopy, with no formal comparison with barium enema yet published. Performance data so far suggest that virtual colonoscopy may surpass the published performance of barium enema for polyp detection, but this is still to be proven. Inherent advantages of the new method over barium enema include no requirement for colon filling with barium, a lack of complex overlapping radiographic lines, no need for a second bowel catharsis before colonoscopy if a polyp is detected, greater patient comfort and acceptance, and the ability to evaluate extracolonic structures and to provide a 'one stop' staging examination of the abdomen and pelvis if cancer is identified. Compared with standard colonoscopy, virtual colonoscopy is associated with a substantially lower risk, has no need for sedation, analgesia or recovery time, has a better patient acceptance, allows the entire colon to be visualized in the vast majority of patients, and eliminates 'blind spots' proximal to colonic folds as the anatomy can be viewed from any perspective. However, an obvious disadvantage of the new method is that tissue cannot be retrieved and all patients with an abnormal test result will require colonoscopy.

Although virtual colonoscopy seems a potentially attractive method of screening for colorectal cancer, many issues must be addressed before it can challenge the existing tests. While initial published results are promising (the findings of several large series are currently in press), they have been achieved in a handful of academic centres and in highly selected patient groups. Large-scale multicentre studies in patients of average risk are planned, and some are currently under way in the USA and Europe. The results of these studies will be crucial to the future of virtual colonoscopy as a screening tool. Considerable effort has been focused on optimizing and standardizing the technique of virtual colonoscopy before commencing these trials, but as both CT and software technologies are advancing rapidly the results of these efforts may be obsolete even before they reach publication. Present research efforts are focused on developing oral barium preparations that opacify residual stool, thereby limiting or even eliminating the need for bowel cleansing. The ability to evaluate the colon without bowel catharsis is likely to have a major impact on the public's acceptance of a screening technique.

It is clear that there is a threshold polyp size (5 mm) below which the performance of virtual colonoscopy drops precipitously, but no clear consensus exists as to the importance of identifying and removing such diminutive polyps. Many of these are hyperplastic with no malignant potential, and for tiny adenomas the risk of malignancy is extremely low. One could argue in favour of a test such as virtual colonoscopy that selectively identifies only medium and large polyps rather than promoting a policy of universal polypectomy. It is accepted that flat adenomas and flat carcinomas exist, but these are difficult to detect with any technique (including virtual colonoscopy).

Ultimately, procedural cost will be a major factor in determining the success of virtual colonoscopy as a screening procedure[10]. As it is a 'diagnosis only' test, it must be provided at a cost not much greater than that of barium enema and less than that of colonoscopy. Using published performance data it has been reported that virtual colonoscopy could be as cost-effective a screening option as colonoscopy if its initial compliance rates were better than that of colonoscopy by 15–20 per cent. For virtual colonoscopy to be successful in population screening an efficient and coordinated collaboration is required between radiologists and endoscopists, whereby patients with normal virtual colonoscopy findings (approximately 80 per cent) are discharged immediately and those with a positive result (approximately 20 per cent) are referred directly for same-day colonoscopy and polypectomy or biopsy, without the need for a second bowel preparation.

In summary, virtual colonoscopy is a promising new technique for imaging the colon. While there appears to be sufficient evidence to support its routine use in patients following failed or incomplete colonoscopy, further evaluation in the form of multicentre trials is required before it can compete on a widespread basis as a colonic cancer screening tool. Current research interest is focused on developing preparations that allow reduced colonic cleansing, thereby improving patient compliance and optimizing the electronic manipulation of data sets to facilitate ease of review and enhance operator performance. Virtual colonoscopy is still a technique in evolution, but the potential for improvement is great.

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Leading article

Aspirin resistance

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Many large trials in cardiac, cerebral and peripheral vascular disease[1,2] have shown that an approximate 25 per cent risk reduction of further serious vascular events can be achieved with aspirin therapy in susceptible individuals, irrespective of the territory of the disease. However, the place of aspirin is now being challenged by the introduction of newer antiplatelet agents and, more recently, by the publication of studies in which such agents are used in combination with aspirin in an attempt to maximize benefit[3,4]. This has reawakened interest in the concept that certain individuals may be relatively 'resistant' to aspirin. Obviously such individuals, if they could be identified, would be candidates for alternative or additional antiplatelet therapy.

Platelet inhibition is not a uniform process and it is well known that there is considerable interindividual and intraindividual variability in aspirin's antiplatelet effect. However, there is no agreement on the frequency of aspirin resistance or, indeed, whether it really exists. There are several factors that may explain this. First, there is no agreed definition of aspirin resistance and its assessment usually requires a specialized platelet laboratory. Second, the dose of aspirin and other agents used also varies between studies, making comparison of antiplatelet activity difficult. The third reason cited by most sceptics to explain aspirin resistance is that it is just a reflection of patient non-compliance with drug therapy; while this may be a significant factor in some individuals it is unlikely to explain all cases of aspirin resistance. In a study of 75 patients admitted with an acute coronary syndrome who received long-term aspirin for secondary cardiac prevention, 26 (35 per cent) were found to be non-responders to aspirin[5]. Of these non-responders only a quarter demonstrated non-compliance with no trace of acetylsalicylate metabolites detected on urinary high-pressure liquid chromatography.

One of the largest studies to examine the prevalence and variation in aspirin resistance involved cerebrovascular disease[6]. The authors followed 306 patients over 33 months and used aggregation studies to define their initial response to aspirin; this response was then followed up in 171 of the original patients, with aspirin dose escalation in non-responders. An initial 25 per cent incidence of aspirin resistance (at a daily dose of 325 mg aspirin) fell to 8 per cent with dose escalation of up to 1300 mg. There was also considerable intraindividual variation in platelet inhibition with time on a fixed dose of aspirin.

Data describing the pharmacokinetics and pharmacodynamics of low-dose aspirin are surprisingly scarce; this is in part due to the drug's age and long time 'off patent'. In one of the few recent pharmacological studies[7], the inhibition of platelet aggregation was found to relate to the area under the plasma concentration *versus* time curve, with considerable intersubject and intrasubject variability in healthy individuals. Aspirin given at any 'effective' dose will potentially cause bleeding complications and so the minimum 'effective' dose is the dose of choice. Quite sensibly, most practitioners have adopted a regimen of using lower doses in the majority of patients with occlusive vascular disease. They do not, however, routinely use any method of assessing whether they are achieving the desired level of antiplatelet effect with these low doses.

The only report that the authors have been able to find relating clinical outcome to aspirin resistance is an Austrian study of 100 claudicants (taking 100 mg aspirin per day) undergoing peripheral arterial angioplasty[8]. Platelet activity was assessed with whole blood aggregometry before and after the procedure. The study demonstrated that reocclusion at the sites of angioplasty occurred exclusively in men for whom aggregometry failed to prove an inhibition of aggregation on stimulation with the agonists adenosine 5′-diphosphate and collagen. Only 40 per cent of men showed the expected effects of aspirin in *ex vivo* platelet studies.

Mechanisms explaining aspirin resistance at a molecular level are currently poorly understood. Glycoprotein IIIa is a membrane receptor of the integrin family that is central to the platelet binding of fibrinogen. Single nucleotide polymorphism of this receptor has been demonstrated to increase platelet aggregation in an allele-dependent fashion[9]. Studies of its clinical relevance, however, remain equivocal[10]. It is likely that the variable response to aspirin originates from a diversity of pathways, all of which have the same final effect of altering aggregation, and that other polymorphisms (such as glycoprotein Ia) also play a role. It has further been suggested that the risk associated with these nucleotide changes may have different implications, depending on an individual patient's coexisting risk factors[11].

If aspirin resistance exists, does it matter and how should it be managed? Increasing the dose of aspirin is one approach, although this will escalate the risk of potential bleeding complications. The advent of newer antiplatelet agents and the option of combination therapy may offer a different avenue in dealing with aspirin resistance. It is the authors' belief that combination antiplatelet therapy will be accepted to reduce vascular events in high-risk patients, but the implications of this will be significant in terms of 'numbers needed to treat' and cost. The ability to select out resistant patients may place us in a position of compromise in which limited finances can be more appropriately directed to those most likely to benefit. Nevertheless, it seems that aspirin therapy will be the primary treatment of choice for the foreseeable future, and it is important in individual high-risk patients that one is confident that aspirin is having the desired effect. There is an urgent need to develop reliable methods of assessing platelet function that are suitable for clinical practice, and to carry out specific studies of aspirin resistance in high-risk patient groups.

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LIBRARY

During July and August 2001 most American surgical journals published a 'Consensus statement on submission and publication of manuscripts, focusing on the issues of duplicate and fraudulent publication. The BJS *supports and endorses this initiative and is pleased to publish these guidelines for the benefit of readers, subscribers and contributors.*

Consensus statement on submission and publication of manuscripts

Surgical Journal Editors Group

Increasing problems of duplicate and fraudulent submissions and publications have prompted the undersigned editors of surgical journals to support these overall principles of publication.

Duplicate submission and publication

In general, if a manuscript has been peer-reviewed and published, any subsequent publication is duplication. Exceptions to this general rule may be:

(a) Prior publication in meeting program abstract booklets or expanded abstracts such as those published by the *Surgical Forum* of the American College of Surgeons or *Transplantation Proceedings*. However, these must be referenced in the final manuscript.

(b) A manuscript that extends an original database (a good rule might be expansion by 50 per cent or more) or that analyses the original database in a different way in order to prove or disprove a different hypothesis. Previous manuscripts reporting the original database must, however, be referenced.

(c) Manuscripts that have been published originally in non-English language journals, provided that the prior publication is clearly indicated on the English language submission and referenced in the manuscript. In some circumstances, permission to publish may need to be obtained from the non-English language journal.

For example, any submission duplicating material previously published in full in 'proceedings' or book chapters is considered duplicate unless the exceptions in (a) above apply. Similarly, manuscripts dealing with subgroups of data (i.e. patients) that have previously been analysed, discussed, and published as a larger group are considered duplicate unless (b) above applies.

The Internet raises special concerns. If data has previously appeared on the Internet, submission of that data for publication is considered duplication. If Internet publication follows journal publication, the journal publication should be clearly referenced. Some journals may provide early Internet publication of accepted peer-reviewed papers that are subsequently published in that journal. This does not constitute duplication if both manuscripts are identical and covered by the same single copyright.

Fraudulent publication

The following activities are examples of fraudulent publication practices:

(a) Wilful and knowing submissions of false data for publication.

(b) Submission of data from sources not the author's (or authors') own.

(c) Falsely certifying that the submitted work is original and has not been submitted to, or accepted by, another journal.

(d) Sponsoring or vouching for a manuscript containing data over which the sponsor has not control or knowledge.

(e) Allowing one's name to appear as an author without having contributed significantly to the study.

(f) Adding an author's name to a manuscript to which he/she has not contributed or reviewed or agreed to in its current form.

(g) Flagrant omission of reference to work of other investigators, which established their priority.

(h) Falsification of any item on the copyright form.

(i) Failure to disclose potential conflict of interest with a sponsoring agency.

While not intended as an all-inclusive document, these examples and guidelines should alert authors to potential problems that should be avoided when they are considering submission of a manuscript to a peer-reviewed journal.

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Restriction enzymes in the analysis of genetic alterations responsible for cancer progression

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Background: Molecular approaches are increasingly being employed to dissect the genetic changes accompanying tumour formation. These methods can often be confusing to the non-specialist as they include complex molecular steps. This can reduce the usefulness of such molecular data to clinicians. The authors aim to aid interpretation of molecular studies in general by presenting a comprehensive review of one molecular approach, i.e. the use of restriction enzymes in molecular studies of tumour development.

Method: A review was made of the molecular studies that have employed restriction enzymes in gastrointestinal cancer research. These studies have used restriction enzymes to analyse point mutation induction, gene methylation status and the deletion of chromosomal loci. In addition, emphasis is placed on some of the important considerations for the molecular analysis of tumours that can affect the molecular data obtained.

Results: Restriction enzyme digestion has played, and continues to play, a major role in analysing the genetic changes in cancer. Many adaptations of basic restriction enzyme methodologies have enhanced the application of this approach in cancer genetics.

Conclusion: The availability of 200 different restriction enzymes, each recognizing different sequences in DNA, has been invaluable in studying cancer genetics. It is hoped that current advances in protein engineering will facilitate the creation of novel restriction enzymes with tailor-made sequence specificities. This will further improve the applicability of restriction enzymes in cancer genetics.

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Introduction

Gastrointestinal tract cancer has been chosen as a model for cancer progression in general. The role of restriction enzymes in unravelling some of the genetic alterations accompanying tumour formation will be highlighted in the following text.

Genetic alterations characterized in gastrointestinal tract cancer

According to the World Health Organization, the combination of colon and oesophageal cancer kills more than 30 000 people each year in the UK[1]; understanding the mechanisms behind these forms of cancer has become a research priority. Much is already known about the progression of these two forms of disease with regard to the identity of the common genetic alterations induced and the associated risk factors. *Table 1* lists the implicated genes, along with some of the identified risk factors. It is hoped, with increased understanding of the genetic basis of gastrointestinal cancers, that diagnostic markers of disease progression may be determined. Such genetic markers might then be employed to screen for high-risk individuals with a view to reducing mortality rates. Although methods already exist that can provide useful information on a range of genetic events, much work will be needed to develop techniques for widespread use in genetic diagnostics.

Gastrointestinal tract cancer, in common with all types of cancer, is induced through the involvement of tumour-specific genes. These key genes fall into three main groups: tumour suppressor genes, oncogenes and modifier genes. It is estimated that four or five different genetic alterations are required to overcome the growth restraints that prevent

Table 1 Genetic alterations implicated in colon cancer and oesophageal cancer, and risk factors for both diseases

	Colon cancer	Oesophageal cancer*
Premalignant stage	Adenoma (hyperplastic polyps)	Barrett's oesophagus
Genes implicated	*APC, K-ras, MCC, DCC, p53*	*p16, APC, p53*
Early events	APC mutation	P53 mutation
Late events	P53 mutation	Aneuploidy
Risk factors	Western diet, age, cigarette smoking	Reflux, obesity, cigarette smoking, alcohol
Protective factors	Exercise, fruit and vegetable diet	Fruit and vegetable diet

*Oesophageal adenocarcinoma, not squamous cell carcinoma

tumour formation in normal cells[2]. Tumour suppressor genes are known to resist the uncontrolled cell proliferation associated with cancer progression. For example, the *p53* gene encodes a protein that arrests the cell cycle when necessary and may induce apoptosis in damaged cells that are at risk of uncontrolled proliferation. Loss of tumour suppressor gene function (by mutation, hypermethylation or deletion) removes this control of cell proliferation and increases the risk of tumorigenesis. Oncogenes (e.g. the *ras* gene family) are involved in the signal transduction pathways that relay growth signals to the nucleus. Mutations in these genes cause continual growth stimulation and allow uncontrolled cell proliferation (amplification of such proto-oncogenes may also induce unrestrained proliferation). Finally, modifier genes (e.g. DNA repair genes) control the general genetic stability of cells, and loss of these genes through mutation, deletion or hypermethylation causes genetic instability in affected cells. For example, defects in the mismatch DNA repair genes in patients with hereditary non-polyposis colorectal cancer predispose these individuals to colon cancer.

When embarking on a genetic study of tumour progression, most researchers begin by analysing the later stages, i.e. the tumour tissue. This is because the genetic alterations are more abundant in tumours and so are more readily detected. In contrast, in premalignant tissue any genetic alterations are masked by the presence of normal DNA from normal cells. It was originally thought that tumour cells, being clonally derived, would contain identical genetic alterations that were responsible for initiating tumour progression. However, it is now accepted, due to the constant genetic evolution that occurs in tumours, that they are genetically heterogeneous[3]. It has been shown that tumour suppressor gene deletions in colonic tumours vary between biopsies of the same tumour[4], demonstrating the non-uniformity of tumour material. Multiple biopsies of tumours may have to be studied because of this tumour heterogeneity. To identify the causative genetic changes in tumour progression, genetic events may need to be identified at earlier stages before tumour instability occurs. Methodologies are required that are capable of identifying early genetic alterations, but the presence of an excess of normal DNA in premalignant tissue provides a substantial challenge for molecular biologists.

Restriction enzymes

Type II restriction enzymes (endonucleases) are bacterial enzymes that have the capacity to identify specific DNA sequences (generally four to six bases) and to cleave DNA at such sites. These enzymes are involved in protecting bacteria from phages (viruses) and function in bacteria in conjunction with methylase enzymes which have identical sequence specificities[5]. The bacterial genome itself is methylated at these recognition sequences thereby preventing the restriction enzymes access to degrade the bacterial DNA; the DNA of invading phages is not methylated and so is readily degraded. Restriction enzymes also recognize and cleave mammalian DNA. Approximately 50 per cent of mammalian DNA contains a restriction site and the capacity of the enzymes to cleave genomic DNA with such sequence specificity has been exploited by molecular geneticists for over 30 years. Restriction enzyme digestion is an essential tool in molecular genetics, allowing the isolation of specific DNA fragments from important species, as well as allowing the cloning and engineering of mutated organisms. These enzymes are employed in the study of genome structure and organization, allow the mapping of genes, and in population studies to analyse sequence differences occurring between individuals. Over 200 type II restriction enzymes have been characterized so far[6], with differing recognition sequences (enzymes sharing the same recognition sequence are known as isoschizomers). *Table 2* shows the characteristics of a number of common restriction enzymes, including those discussed in this review.

Restriction enzymes in cancer research

The advent of the polymerase chain reaction (PCR)[7] has allowed unprecedented access to the DNA sequence of cancer cells. The combination of the amplification power of

Table 2 Restriction enzymes commonly used in molecular genetics

Name	Recognition sequence	Host bacteria	Temperature	Methylation sensitivity
EcoRI	GGATCC	*Escherichia coli*	37°C	Insensitive
MspI	CCGG	*Moraxella* sp.	37°C	Insensitive
HpaII	CCGG	*Haemophilus parainfluenzae*	37°C	Cannot cut methylated CpG
TaqI	TCGA	*Thermus aquaticus*	65°C	Insensitive
ApaI	GGGCCC	*Acetobacter pasteurianus*	25°C	Insensitive
BfaI	CTAG	*Bacteroides fragilis*	37°C	Insensitive
HaeIII	GGCC	*Haemophilus aegyptius*	37°C	Insensitive
HhaI	GCGC	*Haemophilus haemolyticus*	37°C	Insensitive
StyI	CCAAGG or CCTTGG	*E. coli*	37°C	Insensitive
MvaI	CCAGG or CCTGG	*E. coli*	37°C	Insensitive
ZmnI	GAAN$_4$TTC	*Xanthomonas manihotis*	37°C	Insensitive
RsaI	GTAC	*Rhodopseudomonas sphaeroides*	37°C	Insensitive

PCR and the sequence specificity of restriction enzymes has facilitated the analysis of DNA sequence changes in tumour cells, allowing dissection of the genetic alterations accompanying tumour progression. Given that mutations occurring at restriction enzyme sites remove the ability of these enzymes to recognize the DNA sequence, it is relatively simple to study mutations in cancer-related genes through the loss of existing restriction sites. Conversely, one can also examine mutations that create new restriction sites. This use of restriction enzymes represents a rapid and inexpensive method of screening large numbers of tissue samples for the presence of tumour-related mutations. This form of analysis is particularly useful when studying restriction enzyme sites that contain mutation hotspots of tumour-related genes. In practice, batteries of restriction enzymes are employed to cover as many of the important hotspot codons of tumour-related genes as possible. This procedure can also be used to detect polymorphisms in susceptibility genes that alter an individual's risk of tumour formation.

As well as detecting point mutations in DNA, the methylation status of genes can also be determined with restriction enzymes. DNA methylation is known to reduce gene expression; it has been implicated in silencing gene expression and hence has the potential to promote tumour progression. Finally, allelic deletion events may also be detected through the loss of existing restriction enzyme sites, thereby allowing loss of heterozygosity (LOH) to be studied.

Restriction fragment length polymorphism-mediated mutation analysis of tumour tissues

The simplest form of mutation analysis using restriction enzymes involves the analysis of restriction fragment length polymorphisms (RFLPs). These RFLPs reflect the loss or gain of a particular restriction site within a PCR-amplified DNA sequence and are detected by digesting the PCR-amplified gene sequences with the relevant restriction enzymes. Differences in observed digestion patterns in tumours compared with the DNA from normal tissue indicate the presence of a mutation. In tumour tissue, restriction enzymes are most usefully employed to detect hotspot mutations when these hotspots fall within existing restriction sites. PCR products bearing mutations in existing restriction sites fail to be digested and are identified by gel electrophoresis. Obviously, as restriction enzyme sites cover less than 50 per cent of the genome[8], not all DNA sequences are available for study with such enzymes. However, given that over 200 restriction enzymes with different recognition sequences exist[6], many hotspot codons in genes implicated in tumour progression are available for study. *Fig. 1* shows a gel image demonstrating the detection of a *p53* hotspot mutation (codon 248) in a tumour sample by RFLP analysis using the enzyme MspI. Codon 248 of the *p53* gene is a hotspot in many tumour types and normally contains the restriction enzyme site Msp I (recognition sequence CCGG). In *Fig. 1*, the mutated tumour DNA is shown to be resistant to digestion with MspI owing to the mutation in MspI's restriction site. DNA with the normal sequence digests with MspI and the heterozygote DNA bears both uncut (mutated) and cut (non-mutated) bands. *Fig. 2* displays the restriction sites available to study other hotspot codons of the *p53* gene. Similar methods may be employed to study mutation in any of the several hundred cancer-related genes. The sequencing of the mutated PCR products identified through RFLP analysis allows identification of the exact position and type of mutation induced. DNA sequencing is the ultimate method of mutation characterization[8] and allows the confirmation of mutation induction, eliminating the

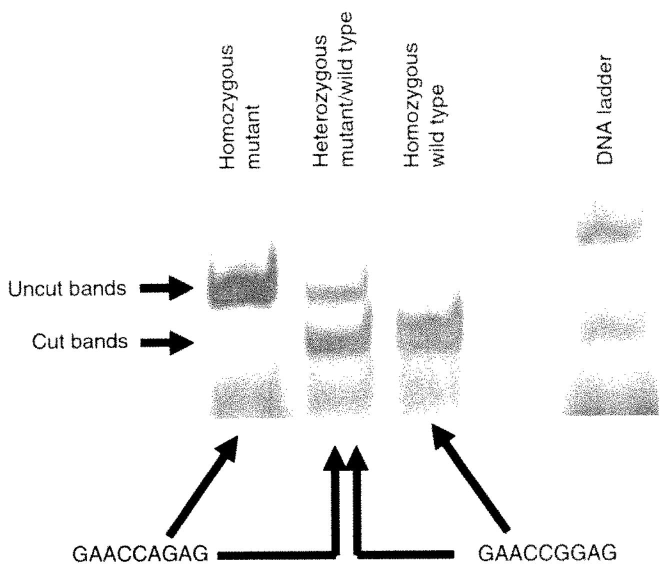
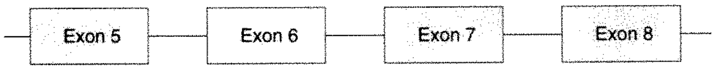


Fig. 1 Schematic representation of restriction fragment length polymorphism analysis to detect mutations in restriction sites with loss of the restriction site (left-hand lane of gel). Digestion of normal sequences with the restriction enzyme is shown in the right-hand lane; heterozygotes contain both digested (wild type) and undigested (mutated) bands (middle lane)



Restriction sites present at the mutation hotspots of the *p53* gene

Hotspot	Codon 175	Codon 213	Codon 248	Codon 282
Sequence	CGC	CGA	CGG	CGG
Restriction enzyme	HhaI (GCGC)	TaqI (TCGA)	MspI (CCGG)	MspI (CCGG)

Restriction sites created by common mutations at hotspots of the *p53* gene

Hotspot	Codon 245	Codon 273
New sequence	AGC	CAT
Restriction enzyme	BST71I (GCAGCN$_9$)	HpyCh4V (TGCA)

Fig. 2 Restriction sites present at the hotspot codons of the *p53* gene suitable for restriction fragment length polymorphism analysis. Restriction enzyme sites created by common *p53* mutations are also shown

possibility that enzyme digestion failure was responsible for the enzyme-resistant PCR product.

Principles similar to those detailed above can be used to screen for the introduction of new restriction enzyme sites in hotspot codons. For example, codon 273 of the *p53* gene is another mutation hotspot in tumours; the most common mutation introduced here alters the sequence surrounding codon 273 from TGCG to TGCA. This is the recognition site of the enzyme HpyCh4V and so PCR products bearing such mutations will be digested by this enzyme, whereas PCR products from normal tissue will not. *Fig. 2* shows some of the restriction enzymes sites created by mutations at hotspot sites within the *p53* gene. Analysing the creation of new restriction sites obviates the need for confirmatory sequencing. Only defined mutational events will create a new restriction site, so the identity of the mutation is already known.

Table 3 Polymorphisms identified in susceptibility genes in colon and oesophageal cancer

Cancer	Gene	Polymorphism	Base change	Amino acid change	Risk (odds ratio)	Reference
Colon	*CYP1A1*	CYP1A1*2A	T to C at 5639	3′-UTR	5·3 (1·0–26·4)	10
Colon	*GSTM1*	Deletion			2·2 (1·5–3·3)	11
Colon	*GSTM1*	Deletion			1·6 (0·9–2·7)	12
Colon	*GSTT1*	Deletion			1·9 (1·3–2·8)	13
Colon	*NAT1*	NAT1*10	T to A at 1088 C to A at 1095	3′-UTR	1·9 (1·2–3·1)	14
Oesophageal	*GSTM1*	Deletion			2·3 (1·8–3·0)	15
Oesophageal	*CYP2E1*	RsaI	C to T at 1017	5′-UTR	3·2 (2·5–4·1)	15

UTR, untranslated region

Analysis of polymorphisms in susceptibility genes that alter individual risk of cancer progression

As well as studying the genes directly responsible for tumour progression, RFLP analysis is widely employed in identifying polymorphisms in susceptibility genes for tumour formation. Polymorphisms (sequence variants representing more than 1 per cent of the population) are present throughout the genome at a frequency of approximately one in every 1000 bases. Recent estimations suggest that there are over 1·4 million sequence variants known as single nucleotide polymorphisms (SNPs) in the human genome. Most polymorphisms are silent, but some lead to modified protein function. These latter polymorphisms may predispose some individuals to tumour formation. This is especially true when the polymorphisms occur in genes involved in carcinogen metabolism, for example carcinogen metabolizing enzymes, such as the cytochrome P450 monooxygenase (CYP450) family, contain polymorphisms that can modulate an individual's risk of tumour progression. Some forms of this enzyme may predispose individuals to a greater risk of tumour formation.

RFLP analysis represents a simple approach to examining SNPs[9]. Hence, the majority of SNPs identified and studied are located within restriction enzyme sites, and are screened for by digestion with the appropriate enzymes. *Table 3* displays a selection of polymorphisms of carcinogen metabolizing enzymes that have been implicated in increasing the risk of oesophageal and colon cancer. The table indicates the increased risk associated with the various genotypes; it can be seen that individuals bearing the 2A genotype of the *CYP1A1* gene have up to a fivefold increased risk of colon cancer.

Detection of the early genetic alterations in tumour formation

A major aim of cancer genetics is to be able to identify the early genetic alterations in premalignant tissue[16], which then act as genetic markers of tumour progression. This should allow the identification of individuals who may be at a higher risk of tumour progression. They may then be enrolled in surveillance programmes or be candidates for surgical intervention. There are two main advantages of studying premalignant tissue. First, the prognosis of patients is much better when the disease is detected early. Second, the genetic alterations in premalignant tissue represent the causative changes in tumour development and are not hidden among other passenger events, as is often the case in tumour tissue.

The methods employed to detect such early genetic markers must be sensitive and rapid to facilitate screening of large numbers of samples for rare sequence changes. The main obstacle in detecting these early changes, as mentioned earlier, is the presence of excess normal DNA. Biopsies of premalignant tissue contain a majority of normal cells, masking the small number of genetically altered cells that are thought to initiate tumour formation. In order to detect these rare genetic alterations, either a large number of individual cells must be analysed separately or some sort of selection applied to the DNA taken from whole biopsy samples to enhance the copy number of the genetically altered DNA. Several PCR-based methods employing restriction enzymes exist that may be suitable for the diagnosis of early mutational events.

Restriction site mutation assay

The restriction site mutation (RSM) assay[17–19] is employed to study mutation prevalence at key hotspot codons of tumour-related genes that fall within restriction enzyme sites and accompany (and may cause) tumour progression. The restriction enzymes suitable for RSM analysis within the *p53* gene are identical to those employed in RFLP analysis (*Fig. 2*). In the RSM assay (*Fig. 3*) restriction enzymes are used initially to digest away the target restriction sites of the normal DNA from biopsy material. After digestion, the remaining uncut (mutated) DNA is PCR amplified using primers flanking the target codon.

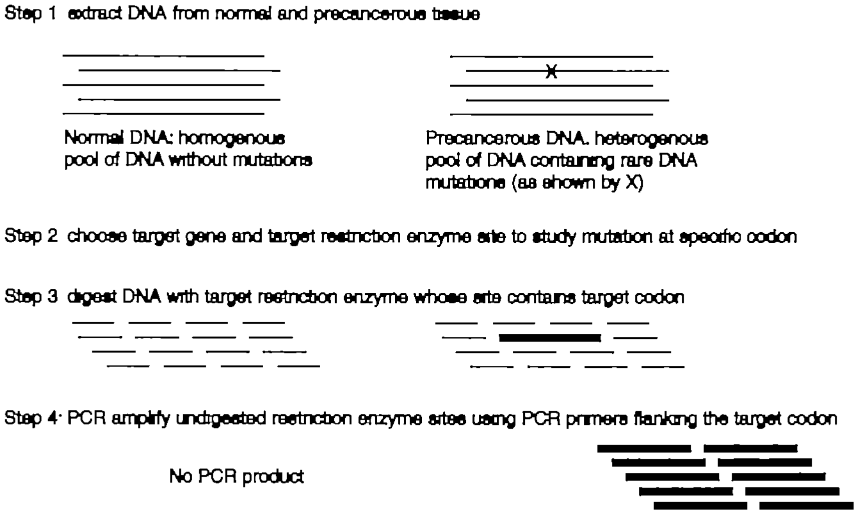

Step 1 extract DNA from normal and precancerous tissue
X
Normal DNA: homogenous pool of DNA without mutations
Precancerous DNA. heterogenous pool of DNA containing rare DNA mutations (as shown by X)
Step 2 choose target gene and target restriction enzyme site to study mutation at specific codon
Step 3 digest DNA with target restriction enzyme whose site contains target codon
Step 4· PCR amplify undigested restriction enzyme sites using PCR primers flanking the target codon
No PCR product

Fig. 3 DNA extracted from precancerous tissue may contain rare mutations that are difficult to detect. The restriction site mutation (RSM) assay is capable of detecting such rare mutations when they occur within restriction enzyme sites. In the RSM assay, DNA is obtained from test precancerous tissue and corresponding control tissue. Subsequent to this, rare mutations can be sought within target genes in the precancerous tissue DNA. A restriction enzyme is employed to digest all the normal sequences at the target restriction enzyme site. Mutated sequences will not digest. As a result of this initial digestion step, excess non-mutated sequences are removed, allowing the subsequent molecular selection of mutated sequences After digestion, polymerase chain reaction (PCR) amplification is performed using PCR primers that flank the target restriction site Only mutated, non-digested DNA will be amplified by PCR

The digested (normal) DNA is unable to be amplified by PCR and so only mutated sequences are amplified. This molecular selection facilitates the enhancement of very rare mutated sequences from within an excess of normal sequences. Undigested (mutated) PCR products are sequenced to ascertain the identity and position of the mutations induced.

The RSM assay, therefore, couples PCR amplification and restriction enzyme digestion differently to RFLP analysis, in order to detect rare mutations. RFLP analysis detects prevalent mutations occurring in restriction enzyme sites in key genes in tumours, but its sensitivity is low (approximately one mutant sequence among ten normal sequences). In the RSM assay this sensitivity is substantially increased. *Fig. 4* shows the results of an experiment employing normal human DNA, spiked with dilutions of tumour DNA containing a *p53* codon 175 mutation (HhaI restriction site), in order to determine the sensitivity of the RSM assay. In this case, using HhaI to distinguish mutated codon 175 DNA from non-mutated codon 175 DNA, mutations present at a frequency of 10^{-4} (one mutated sequence among 10 000 normal sequences) were detectable, indicating the sensitivity of the RSM assay in this instance. The strength of the undigested band can also be used to estimate the prevalence of the mutation in the biopsy sample (high prevalence – strong band, low prevalence – weak band). With the concurrent use of DNA standards containing known amounts of the target gene, the number of mutated copies of the target restriction site can be estimated. This knowledge of the prevalence of the mutation in clinical biopsies may prove important in the clinical management of patients.

This approach has been optimized and validated through the detection of rare mutations induced in animal models and in cultured human cells after exposure to known mutagens[20–24]. Furthermore, the method has been used to analyse the presence of mutations in key tumour-related genes in clinical samples. The RSM assay has yielded early *p53* mutational information in clinical samples of inflammatory colon tissue[25,26]. From these data it may be concluded that *p53* mutational events are early (perhaps initiating) events in cancer related to inflammatory colonic disease. The data also show that inflammatory colon cancer differs from the common adenoma–carcinoma sequence, in which *p53* mutation is a late event[2].

A drawback with both the RSM assay and with RFLP analysis is that these methods are tied to studying mutation induction solely at restriction sites. Unfortunately, hotspot sites for tumour-specific mutations do not always conveniently fall within restriction enzyme sites. However, current developments have overcome this limitation.

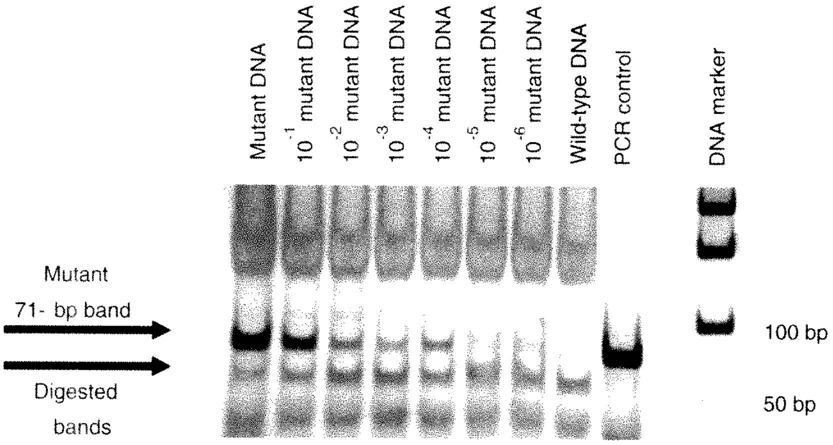


Fig. 4 Sensitivity of the restriction site mutation (RSM) assay. Normal DNA was spiked with tumour DNA bearing a codon 175 *p53* mutation; these dilutions were subsequently analysed by RSM using the HhaI site of codon 175. The detection limit (sensitivity) of the assay was determined to be approximately 10^{-4} (i.e. one mutation among 10 000 normal sequences). PCR, polymerase chain reaction; bp, base pair

Artificial restriction site analysis

To overcome the lack of restriction sites at key codons of tumour-related genes and to harness the ease of restriction enzyme-mediated mutation analysis, methods have arisen to introduce restriction sites artificially where required[27–31]. These facilitate mutation analysis with restriction enzymes at practically any sequence. *Fig. 5* shows the methodology employed in the case of the K-*ras* gene. In this method, one PCR primer is designed to create an artificial MvaI restriction site in the hotspot codon 12 of the K-*ras* gene, by annealing a mismatched primer at codon 11. Normal K-*ras* DNA amplified with this primer will subsequently digest with the MvaI restriction enzyme owing to the creation of this artificial site. However, if mutations are induced in codon 12, this artificially created restriction site is lost and the PCR products fail to digest with MvaI. Undigested PCR products are subsequently sequenced to ascertain the mutations therein. Given that K-*ras* mutations causing tumour formation occur at a small number of hotspots (more than 80 per cent occur at codon 12), screening for such mutations is feasible in tumour tissues.

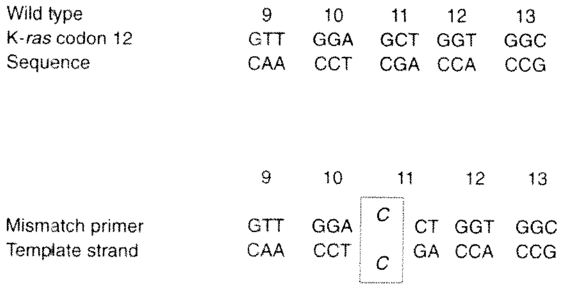


Fig. 5 Artificial restriction site analysis at codon 12 of the K-*ras* gene. A mismatched primer introduces a G to C alteration in codon 11, producing an MvaI (CCTGG) site at codon 12. Normal DNA amplified by polymerase chain reaction (PCR) with this mismatched primer will digest with MvaI after PCR. This MvaI site is lost if mutations are present in codon 12, as is often the case in colon cancer

Fig. 6 shows a representative gel of normal DNA spiked with differing amounts of mutated K-*ras* DNA. It is clear that the sensitivity of this method is approximately one in 1000 (i.e. approximately ten times less than that of the RSM assay). Previous studies employing this methodology have shown that K-*ras* mutations occur in 30–60 per cent of colorectal cancers[32], but are rare events in upper gastrointestinal tract cancer[33]. Indeed, comparative studies of K-*ras* mutation prevalence in upper and lower gastrointestinal tract cancers employing this methodology have shown that lower tumours possess tenfold more K-*ras* mutations than upper tumours[34]. Studies have also shown that K-*ras* mutations are nearly as common in hyperplastic polyps (47 per cent) as in adenomatous adenomas (56 per cent)[35], suggesting a common pathway in cancer progression for these premalignant lesions. In addition, this methodology has been shown to be capable of detecting the presence of tumour DNA circulating in blood plasma. As tumour cells are degraded, the DNA from these dead cells enters the blood and is detectable in the plasma at a concentration of

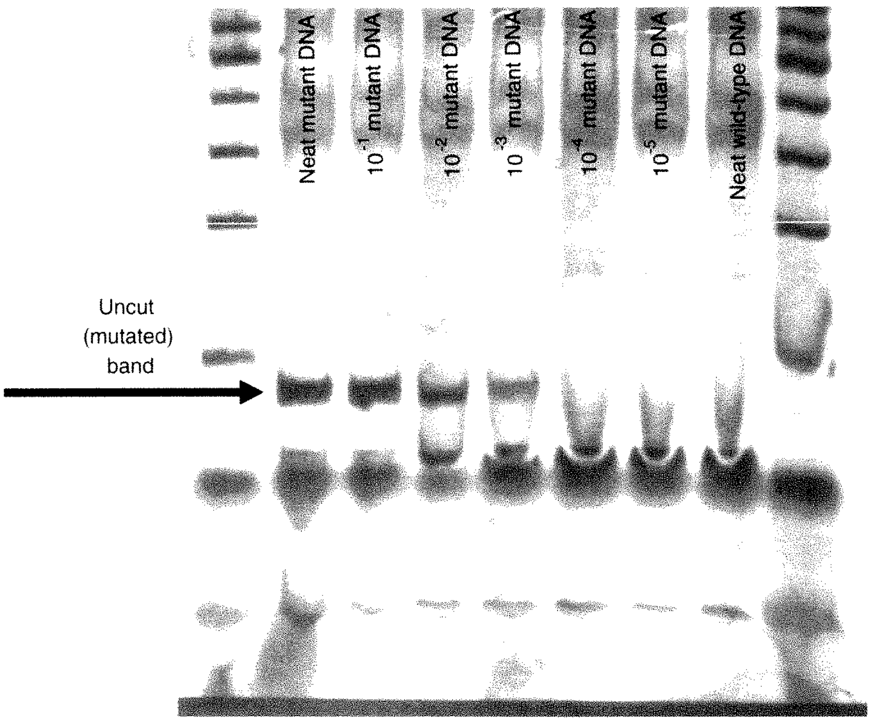


Fig. 6 Detection limit (sensitivity) of the artificial restriction site method. Normal DNA was spiked with dilutions of tumour DNA bearing a K-*ras* codon 12 mutation. The undigested polymerase chain reaction products (mutations) are detectable even when a 1000-fold excess of normal sequences is present

approximately 10 ng/ml[36,37]. Several studies have identified DNA sequences containing identical K-*ras* mutations in both tumour and plasma[37–39]. Indeed, studies employing artificial restriction site analysis have shown that plasma DNA can be used to detect tumour-specific mutations in more than 80 per cent of patients analysed[37,38]. Hence, for gastrointestinal tract cancers, blood may offer a non-invasive source of tumour markers which can be used to screen patients for tumour progression, tumour size and an individual's response to cancer therapies.

This artificial restriction site methodology can be extended to study just about any codon (of any gene) for the presence of known mutation hotspots by using mismatched primers and one of the 200 or so commercially available restriction enzymes[6].

DNA methylation studies

Genomic DNA methylation silences gene expression[40]. Human DNA methylation occurs at cytosine bases in CpG sequence contexts (often in so-called CpG islands). CpG sites are merely CG sequences which are prone to methylation. These CpG islands occur upstream of the transcription start sites of genes and interact with the transcription machinery when methylated, thus preventing transcription. Key genes in tumour-specific pathways may therefore be lost through deletion, mutation or by hypermethylation[41]. Conversely, hypomethylation allows the expression of genes that would normally be silent.

Restriction enzymes can be employed to study DNA methylation patterns and this can yield important information in cancer research[42]. Pairs of restriction enzymes may be employed in methylation studies which recognize the same sequence in DNA, but differ in their sensitivity to methylation, e.g. MspI and HpaII (both recognize the CCGG sequence). The MspI enzyme is insensitive to methylation (i.e. it cuts both methylated and unmethylated DNA). However, HpaII digestion is blocked by methylation and HpaII will only cut unmethylated DNA. *Fig. 7* demonstrates the differential sensitivity of HpaII and MspI to methylation. PCR products from exon 7 of the human *p53* gene were methylated *in vitro* using the SssI methylase enzyme. Methylated and unmethylated PCR products were subsequently digested with MspI and HpaII. The results shown in the figure demonstrate that HpaII fails to digest the methylated DNA, whereas MspI is insensitive to methylation status.

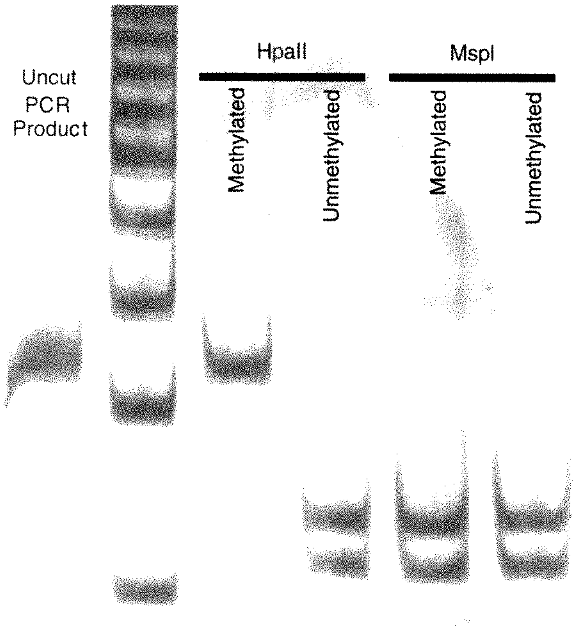


Fig. 7 Use of restriction enzymes to detect DNA methylation. Here, polymerase chain reaction (PCR) products of exon 7 of the *p53* gene were methylated *in vitro* by SssI methylase. Methylated and unmethylated PCR products were then subjected to digestion with MspI and HpaII. Note that HpaII is blocked by DNA methylation, whereas MspI digests

This phenomenon can be exploited to identify alterations in methylation status of promoters bearing CCGG sequences which accompany cancer progression. The digestion of genomic DNA with HpaII before PCR amplification with primers flanking the promoter region will distinguish methylated from non-methylated DNA (methylated DNA will resist digestion and yield a PCR product, whereas non-methylated DNA will digest and fail to yield a PCR product). In this manner the methylation status can be compared between tumours and non-tumour tissue to assess the role of altered methylation of key genes in tumour progression. Methylation studies have been employed to analyse the silencing of key genes in gastrointestinal tract cancer. For example, methylation of the mismatch repair gene *MLH1* removes protein function and leads to microsatellite instability (MSI) in 70 per cent of sporadic colon tumours studied[43]. Indeed, *MLH1* methylation has been detected in nearly 50 per cent of tumours with high levels of MSI and may represent an alternative to mutation induction in removing MLH1 function[44]. In addition, methylation of the cyclin-dependent kinase inhibitor gene P16 has been shown to be an important early step in upper gastrointestinal tract cancer, being present in over 80 per cent of oesophageal tumours[45]. However, *p16* methylation is rare in colon cancer[46], highlighting the different genetic pathways involved in upper and lower alimentary tract cancer.

Loss of heterozygosity analysis

Restriction enzymes have also been used to study allelic losses (deletion events) with a technique called LOH analysis. During carcinogenesis, mutation often occurs in one allele of a tumour suppressor gene, followed by the loss of the remaining allele by a deletion event. As noted above, DNA polymorphisms are common in genes; this is also true for tumour-related genes. The existence of these polymorphisms in restriction sites can be exploited in detecting allelic losses in tumours. When individuals are heterozygous for a tumour gene polymorphism (i.e. contain two different alleles), they can be screened for losses of alleles by restriction digestion; homozygous individuals cannot be studied. Normal tissue from heterozygous individuals contains two DNA sequences, one that digests with the restriction enzyme and one sequence that does not digest. So PCR-amplified DNA will possess three bands after digestion, one uncut band and two cut bands. Tumour tissue from the same individual should also possess three bands but if one allele has been deleted, either the cut bands or the uncut band will disappear, indicating LOH. *Fig. 8* shows a representative gel demonstrating LOH analysis using restriction digestion. These methods have shown the importance of tumour suppressor gene deletions in tumour evolution, for example LOH has been shown in patients with Li–Fraumeni syndrome who possess heterozygous mutations within the *p53* gene[47]. Given that polymorphisms occur approximately every 1000 bases, the *p53* gene, which is almost 20 000 bases long, will contain approximately 20 polymorphisms. Only one of these needs to be within a restriction site for LOH analysis to be performed. *Table 4* shows some of the polymorphisms identified in tumour suppressor genes that allow LOH analyses by restriction enzyme digestion. A list of *p53* polymorphisms is also available at the World Health Organization International Agency for Research on Cancer website[1].

Important considerations for molecular analysis of tumour progression

For molecular analysis of tumour development to be useful in determining the genetic changes driving carcinogenesis, the methods employed must be robust and reliable; the results must be reproducible. When performing molecular analyses of tumour/premalignant tissue, there are several stages at which problems may arise. These stages include

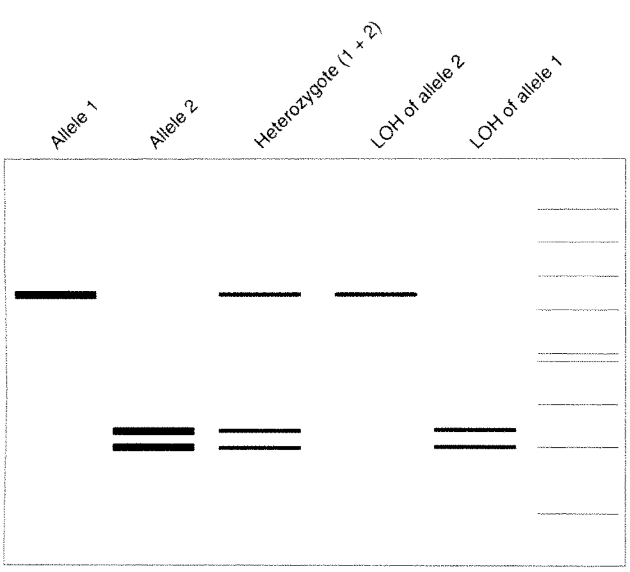


Fig. 8 Representative gel showing how restriction sites can be used in loss of heterozygosity (LOH) analysis. If an individual is heterozygous for a polymorphism in a tumour suppressor gene restriction site, after polymerase chain reaction and digestion there is a mixture of undigested (lane 1) and digested (lane 2) bands, and a pattern similar to that of lane 3. If a tumour from that individual has lost a copy of the tumour suppressor gene in question one of the alleles (digestible or indigestible) will be lost

Table 4 Polymorphisms in tumour-related genes allowing loss of heterozygosity analysis

Gene	Polymorphism location	Restriction site	Reference
p53	Intron 7	ApaI (GGGCCC)	48
p53	Intron 6	MspI (CCGG)	49
DCC	Codon 201	SalI	50
p73	Exon 2 (UTR)	StyI (CCAAGG or CCTTGG)	51

UTR, untranslated region

the source of the DNA, the extraction of the DNA, the PCR amplification of tumour DNA, and the DNA sequencing (in the case of mutational events).

DNA for genetic analysis may be obtained from fresh tissue, frozen tissue or archival tissue (usually paraffin-embedded tissue sections). DNA quality is highest from fresh tissue and lowest from tissue sections; the quality of DNA from frozen tissue depends on the duration of storage and the temperature of freezing. The method of DNA extraction is also a source of concern in some studies. Modern DNA sequencing equipment can be damaged by the presence of trace amounts of phenol, a common solvent used in DNA extraction. In addition, phenol/chloroform extraction can introduce oxidative damage into DNA[52] that can subsequently introduce artefactual mutations in the DNA during PCR. Other techniques, such as high-salt DNA extraction methods, may be preferable in some instances.

Most molecular methodologies employed to detect genetic alterations in tumour progression rely on PCR amplification. A main concern is that the copying of DNA during amplification is prone to errors. These are caused by Taq polymerase which induces these errors at frequencies of one in every 10^4–10^5 bases copied[53–56]. If these errors are induced early in the PCR amplification, they may comprise a significant proportion of the final PCR product and be mistaken for mutational events present in the cells analysed, i.e. produce false-positive mutations. Defined conditions to reduce the chance of Taq error (e.g. use of high-fidelity polymerases) should be included in PCR regimens. In addition, duplicate PCR products should be analysed from each sample where possible, as the chance of a similar Taq error occurring in two independent reactions is minimal.

A similar concern in the molecular analysis of tumour progression relates to the accuracy of DNA sequencing reactions. Sequencing errors result from the polymerase enzyme arresting at particular bases within the sequence (usually those containing secondary structure), resulting in false peaks on the sequence gels which may be misconstrued as mutations. There is evidence that some of the hotspot regions of the *p53* gene are prone to sequencing errors, in particular codons 273 and 283[57]. An example may be given from the authors' laboratory of a sequencing artefact obtained in a hotspot codon of the *p53* gene (codon 196) of a colon tumour. In this case, one strand of the PCR product bore a mutation, while the other strand possessed the normal sequence. This particular codon 196 mutation would have introduced a new BfaI restriction site (CTAG) at codon 196 and so digestion of the PCR-amplified tumour DNA with this enzyme was used to confirm that this mutation was not present in the tumour DNA and was, therefore, a sequencing artefact. This confirmation of sequence alterations represents yet another application of restriction enzymes. Given the large number of restriction enzymes available, mutational events often involve the loss or creation of particular restriction sites. Because restriction enzyme digestion is cheaper and quicker than resequencing, it can be more effective at confirming mutational events. It is imperative that both strands of DNA are sequenced to ensure that any mutation appears on both strands and is not an artefact of a single-pass sequencing reaction. It is not known to what extent the current literature contains mutation data resulting from poor sequencing and so may contain mutational artefacts. Caution must be exercised when relying on sequence data from the literature or from mutation databases.

Conclusion

The various applications of restriction enzymes in cancer research have been described and these have been illustrated with examples of genetic data on the progression of two types of gastrointestinal cancer. Restriction enzymes have been used in a number of genetic studies and have provided information on tumour-specific mutations, rare mutations in premalignant tissue, and polymorphisms in cancer susceptibility genes. As well as detecting mutational events, these enzymes have also been employed to detect LOH and altered methylation patterns in cancer development. The reason for the widespread employment of restriction enzymes in cancer research is twofold. First, because of their sequence specificity, they are remarkable molecular tools that allow the study of DNA at the nucleotide level. Second, owing to their ubiquitous use in various molecular genetic applications over the past 30 years, many restriction enzymes have been characterized and are now commercially available as high-quality enzyme preparations, accompanied by detailed knowledge of their optimum digestion conditions. With recent advances in protein engineering, it may be possible in the near future to alter the sequence specificity of restriction enzymes, thereby tailoring them for particular sequence specificity. This may further extend the applicability of restriction enzyme technology in the study of molecular carcinogenesis.

Acknowledgements

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P, 25, 319.

Review

Sentinel lymph node biopsy and breast cancer

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Background and method: This paper reviews and discusses the feasibility and accuracy of sentinel lymph node (SLN) biopsy in breast cancer. A standardized method of identifying the SLN and detecting micrometastases is suggested, along with a strategy for the elimination of routine axillary lymph node dissection (ALND).

Results: Although the SLN can be identified successfully by experienced practitioners using either the dye-guided or γ probe-guided method, identification is facilitated when the two techniques are combined. To improve the likelihood of spotting metastases in the SLN, it is desirable to perform step sectioning combined with haematoxylin and eosin staining and immunohistochemistry of permanent and frozen sections. SLN biopsy is as accurate for T_2 tumours as it is for T_1 tumours. However, it is highly unlikely that all false-negative cases can be eliminated, even by detailed histological examination. Nevertheless, patients with T_1 tumours with micrometastases in the SLN have shown no evidence of tumour in the non-sentinel nodes. In other words, ALND can be avoided in these patients, even if histological examination of the SLN fails to detect micrometastasis.

Conclusion: In practice, routine ALND can be avoided in patients with T_1 tumours when the identified SLN proves to be histologically negative. However, investigation of long-term regional controls and of survival in a prospective randomized trial is necessary before SLN biopsy can replace routine ALND, particularly for patients with T_2 tumours.

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Introduction

Sentinel lymph node (SLN) biopsy has been developed to assess accurately the axillary nodal status without removing most of the axillary contents[1–6]. The SLN is defined as the first node in the lymphatic basin that receives the primary lymphatic flow. A tumour-negative SLN virtually excludes lymphatic involvement of the entire regional lymphatic basin[7], rendering axillary lymph node dissection (ALND) unnecessary in patients with node-negative breast cancer. SLN biopsy is likely to be one of the most exciting advances in the surgical management of breast cancer since the advent of breast-conserving treatment. It results in fewer ALND-related complications[8], shorter hospital stay, cost reduction[9] and a more accurate indication for treatment with adjuvant therapy[10].

Because SLN technology has been evolving rapidly, variations in technique have become widespread and no standard procedure has yet been established. Numerous controversial issues concerning the optimal method for identifying the SLN, detecting micrometastases and obviating routine ALND remain unresolved. Specific issues include (1) pros and cons of the dye-guided, γ probe-guided, and dye- and γ probe-guided methods; (2) optimal particle size of radioisotopes, and dose and volume of radioisotopes; (3) advantages of peritumoural *versus* subdermal or subareolar injection; (4) efficacy of preoperative lymphoscintigraphy; (5) relevance of internal mammary SLN biopsy; (6) most suitable method for histological SLN examination; (7) intraoperative diagnosis of SLN (frozen section *versus* cytological examination); (8) clinical significance of micrometastases; and (9) patient selection for avoiding ALND in clinical practice. So SLN biopsy must still be considered as experimental; it has not been introduced as a routine procedure in most institutions. The growing demand from patients for less invasive procedures, however, has created a considerable incentive for accepting SLN biopsy without ALND as standard practice. In the light of this, consistency of technique and case selection have attained great significance. The objectives of this article are to review current knowledge of SLN biopsy in breast cancer, to discuss existing controversies, and to suggest a method for the identification of the SLN and the detection of micrometastases in the SLN in order to eliminate routine ALND.

Identification of sentinel lymph nodes

Blue dye, radioisotopes, or a combination of blue dye and radioisotopes

SLNs have been identified by using blue dye[1,2], radioisotopes[3–5], or a combination of blue dye and radioisotopes (*Fig. 1*)[6]. However, the debate continues as to which method is best[11,12]. In a major series, Cox *et al.*[13] reported that blue dye helped identify SLNs in 80 per cent and radioisotopes in 89 per cent of patients. Using a combination of blue dye and radioisotopes increased the success rate to 96 per cent. Cody *et al.*[14] identified SLNs by blue dye in 81 per cent of patients, by radioisotopes in 87 per cent and by the combined technique in 95 per cent. In a multicentre study by the Japanese Breast Cancer Society, SLNs were identified successfully in 94 per cent of patients by using the combined technique, but in only 74 per cent by blue dye alone[15]. Similarly, an overview by Cody[16] and a meta-analysis by Miltenburg *et al.*[17] both described a higher identification rate of SLNs with the combined technique compared with blue dye or radioisotope alone. This improvement in the identification rate may well reflect retrospective learning by surgeons, but it may also be related to a true benefit of the combined technique.

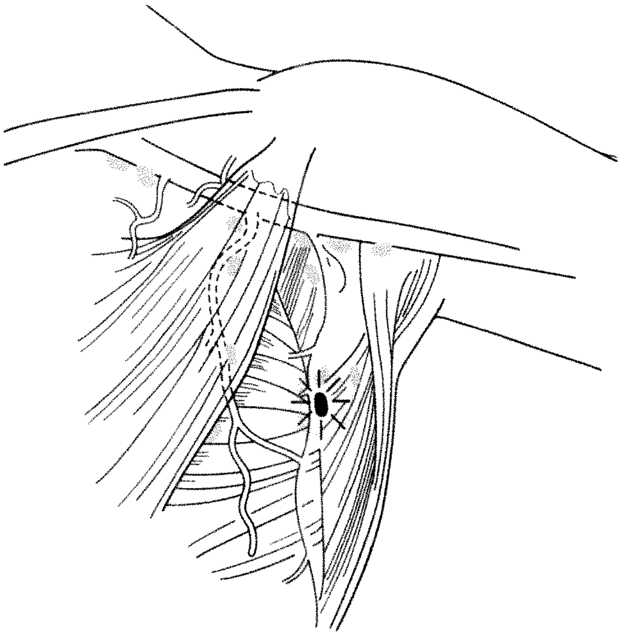

Fig. 1 Axillary lymph nodes (yellow); hot and blue sentinel lymph node (shown in black above)

A randomized clinical trial was conducted to compare results with blue dye alone with those obtained with the combination technique[11]. Morrow *et al.*[11] reported that there were no significant differences between these two techniques in terms of rate of SLN identification (88 and 86 per cent respectively) or in the time needed for SLN identification (8·2 and 9·6 min respectively). The most important predictor of SLN identification accuracy was the number of cases examined by an individual surgeon. Nevertheless, their conclusion that there is no advantage in using dye plus radioisotopes remains controversial. The success rate of SLN identification using a combination of blue dye and radioisotopes was relatively low in this randomized study compared with others[13,14,16,17]. The use of radioisotopes, moreover, can sometimes result in a smaller incision and less dissection. Currently, many investigators believe that the blue dye and radioisotope techniques are complementary, and that SLN identification is facilitated when the two techniques are used together[6,14–16,18–20].

Dyes

A number of dyes have been tested for SLN identification. Isosulfan blue is readily available as a blue dye tracer in the USA[1,6,20,21], while patent blue violet is mostly used in Europe[22]. Isosulfan blue is the monosodium salt of 2,5-disulphonated triphenyl methane, while patent blue violet is a triphenyl methane similar in structure to isosulfan blue. Biochemically, they are essentially the same agents, and no difference has been observed in their ability to identify SLNs[23].

Other dyes, including methylene blue, indocyanine green and indigocarmine, have also been used by some investigators[15,24]. However, methylene blue should be avoided as one of the known complications of injecting this drug is fat necrosis in patients who have had breast conservation surgery. In Japan, patent blue violet, indocyanine green and indigocarmine are commonly used because isosulfan blue is not commercially available[15]. The SLN identification rate was not significantly different between these three dyes in a multicentre study by the Japanese Breast Cancer Society[15]. While no prospective clinical study has yet been conducted to compare these dyes, it seems that surgeons using a variety of dyes can expect to achieve a reasonable rate of technical success[15].

Optimal particle size of radioisotope tracers

The optimal size of a radioisotope tracer for SLN identification has remained controversial[12]. One of the biggest potential difficulties is that small particle tracers may pass through the SLN and label secondary nodes. A particle size of 3–30 nm is considered effective for lymphoscintigraphy, but the ideal radioisotope tracer for SLN visualization is clearly different from a particulate tracer optimized for the visualization of all lymph nodes by means of scintigraphy[25–27]. Large particle tracers, on the other hand, appear to pass through to secondary nodes rarely, but they show less uptake at the injection site.

European studies have employed ^{99m}Tc-radiolabelled colloidal albumin[4,28,29]. Paganelli *et al.*[28] demonstrated that the SLN can be identified more easily by using large particle colloidal albumin rather than small particle radioisotopes. Several nodes could be visualized at the axilla by means of lymphoscintigraphy using microcolloids of sulphide (particle size less than 50 nm) or colloids of human serum albumin (particle size less than 80 nm). Conversely, only one node was identified when colloids of human serum albumin (particle size 200–1000 nm) were used. In this last group of patients, the surgeon was able to identify SLNs more easily and in a shorter time by using a γ probe. Subsequently, Veronesi *et al.*[29] used microcolloidal albumin in a later study, while they used nanocolloidal albumin in their initial study[4].

American investigators have used ^{99m}Tc-radiolabelled sulphur colloid[16,30,31] because ^{99m}Tc-labelled colloidal albumin is not commercially available in the USA. In the initial studies the ideal size of the radioisotope tracer was thought to be between 10 and 200 nm[16,26,32] and so ^{99m}Tc-radiolabelled filtered sulphur colloid (particle size less than 200 nm) was used. However, some investigators[30,31] have suggested that unfiltered ^{99m}Tc-labelled sulphur colloid is preferable. Linehan *et al.*[31] identified SLNs in 68 (88 per cent) of 77 cases when unfiltered ^{99m}Tc-radiolabelled sulphur colloid was used and 42 (74 per cent) of 57 cases with filtered ^{99m}Tc-labelled sulphur colloid, but the difference did not reach statistical significance ($P = 0{\cdot}051$).

In Japan, neither ^{99m}Tc-radiolabelled sulphur colloid nor ^{99m}Tc-radiolabelled colloidal albumin is commercially available, forcing Japanese investigators to use either ^{99m}Tc-labelled human serum albumin or ^{99m}Tc-labelled tin colloid. However, ^{99m}Tc-radiolabelled human serum albumin (particle size 2–3 nm) is too small, migrates very rapidly and tends to overflow to non-SLNs[15,25,33], so that most Japanese investigators have used ^{99m}Tc-labelled tin colloid (particle size 400–5000 nm) in their studies[15,34]. Nevertheless, the size of the latter is too large, as may be appreciated by the relatively low success rate for visualization of SLNs by lymphoscintigraphy[35]. Recently, ^{99m}Tc-radiolabelled stannous phytate (particle size 200–1000 nm), which is commercially available in Japan, has been used, leading to an improved SLN identification rate (82–100 per cent compared with 67 per cent for ^{99m}Tc-labelled human serum albumin and 36–63 per cent for ^{99m}Tc-labelled tin colloid (M. Noguchi, unpublished data)).

The use of medium particle radioisotope tracers (particle size 200–1000 nm) is preferred because the SLN identification rate is relatively high and only one or two SLNs can be identified even the day after injection[28]. This approach avoids the unnecessary removal of non-sentinel nodes.

Optimal time for radioisotope injection

The radioisotope tracer flows to and concentrates in the SLN, creating a 'hot spot' compared with the surrounding tissues. The time of the injection is not critical, however, as long as there is adequate time to allow the radioisotope to migrate into the SLN. A reasonable window for harvesting SLNs is 2–24 h from the time of radioisotope injection[28,36–41].

Lymphoscintigraphic studies have shown no axillary uptake in 16–79 per cent of patients 2·0–2·5 h after injection[36,38], suggesting that radioisotopes should be injected at least 2–4 h before surgery to ensure that all potential SLNs will be detected by the γ probe. However, Schneebaum *et al.*[37] demonstrated SLN identification by lymphoscintigraphy 24 h after injection of 60 MBq ^{99m}Tc-radiolabelled rhenium colloid (particle size 50–100 nm). These images were identical to those seen after 2 h. Other authors[4,28,29,36,39,41] have also reported that the SLN could be identified the day after injection and so it is possible to carry out the SLN biopsy then. This is convenient for surgeons with a tight operating room schedule[41].

Dose and volume of radioisotope tracer

The doses have ranged from 7 to 370 MBq[12]. Krag *et al.*[30,42] recommend a standardized activity of 37 MBq, although they initially used a dose of 15 MBq[3]. They suggest that using 37 MBq (1 mCi) results in a technically easier procedure, since counts are higher and the SLN is easier to detect with a γ probe[30,42]. However, a dose of 11 MBq (0·3 mCi) was found to be equally effective for most patients receiving a peritumoural isotope injection in another study[43]. In other studies[29,44] the SLN could be identified with the γ probe even 24 h after the injection of 7 MBq (0·2 mCi) of ^{99m}Tc-radiolabelled colloidal albumin. A smaller radioisotope dose is advantageous because the 'shine through' from the high level of radioactivity at the tumour site may obscure a 'hot spot' in either the axilla or the internal mammary node[45], while unnecessary radiation exposure of the surgeon and hospital staff is avoided.

Another variable is the volume of fluid containing the radioisotope that should be injected. Volumes have ranged from 0·2 to 8 ml, a difference of a factor of 40[12].

Investigators who use a small volume argue that they want to avoid disturbing the physiology of lymphatic flow and the risk of visualizing non-SLNs[29,44]. Moreover, it has been suggested that injection with a volume of 0·1–0·3 ml reduces the 'shine through' effect[45,46]. Because the lymphatic channels are much richer at the subdermal level than at the peritumoural site, a smaller volume of tracer might be adequate to identify the SLN in the case of subdermal or subareolar injection. On the other hand, investigators using larger volumes actually want to change the physiology by increasing the lymphatic flow to enhance visualization of the SLN[30,47,48]. Since large particles migrate poorly within the lymphatics, larger volumes of injection (4–8 ml) facilitate lymphatic uptake via maximal distension of the anchoring filaments[27], and increase the identification success rate for axillary[30] as well as extra-axillary[47] SLNs. Krag *et al.*[30] reported a higher identification rate when the volume was increased from less than 3 ml to more than 8 ml for peritumoural injection. A larger volume may well be necessary for peritumoural injection, but this study was not performed in a randomized fashion, and results are likely to improve with learning through experience no matter what technique is used. Although tracer volume remains controversial, detection rates seem to be good with either smaller or larger volumes of tracer fluid[49]. A disadvantage of a large volume, however, is an increase in the diffusion zone at the injection site, which hampers lymphoscintigraphy and probe detection of nearby nodes[50].

Injection site of dye and radioisotope tracer: peritumoural, subdermal or subareolar

Techniques for the administration of dye and/or radioisotope in breast cancer include intratumoural, peritumoural (parenchymal) and subcutaneous (intradermal, subdermal or subareolar) injection. The optimal injection site of dye or radioisotope tracer for localizing the SLN remains a matter of debate[12]. Since the goal of SLN biopsy is to identify the node draining directly from the tumour, it makes sense to inject the tracer into the lesion[51], but there is a potential danger of needle tract seeding by using the intratumoural method[51,52].

Most of the earlier studies of SLN biopsy for breast cancer involved injection directly into the parenchyma of the breast around the tumour[3,5,6]. However, this procedure now appears to be associated with technical problems of inconsistent preoperative or intraoperative SLN identification because of the significant 'shine effect' from the peritumoural injection site, especially in the upper outer quadrant. The challenge, therefore, has been to improve the injection site to maximize the identification of the SLN and minimize the 'shine effect'. Several studies have been performed in which the blue dye or radioisotope tracer was injected either under or into the skin overlying the tumour[4,22,45,53] or into the subareolar tissue[54,55].

The subdermal or intradermal approach is based on the idea that the skin overlying the breast parenchyma has the same embryological origin as the underlying tissue and so should share the same lymphatic drainage pattern. Borgstein *et al.*[22] used intradermal blue dye and radioisotope injection around the lesion to demonstrate complete concordance between the lymphatic drainage of a breast tumour and its overlying skin. Veronesi *et al.*[4] and Roumen *et al.*[53] also reported that SLN localization by dermally injected radioisotope can predict axillary nodal status as accurately as can peritumoural injection. Similarly, Linehan *et al.*[45] showed that the dermal and parenchymal lymphatics of the breast drain into the same SLN in most patients. In their study, isotope SLN localization was successful in 78 per cent with peritumoural injection and 97 per cent with intradermal injection ($P < 0{\cdot}001$)[45]. They therefore suggested that intradermal injection may simplify and optimize SLN localization because it is easier to perform and more effective. Nevertheless, a warning has been issued that injecting the tracer further away from the tumour increases the risk that a lymphatic watershed is crossed and that the node that is visualized is not the node that drains the tumour (regional mismatch)[56].

The subareolar approach is based on studies indicating that this area provides a central access route to the peripheral lymphatic pathways[54,55]. In a study by Klimberg *et al.*[54] subareolar radioisotope injection produced results as accurate as those obtained with peritumoural injection of blue dye. Of the 69 lesions they examined, SLNs were located in 62 (90 per cent) with the blue dye and in 65 (94 per cent) with the radioisotope. All blue SLNs were also radioactive, but the SLN could not be located with either method in the remaining four patients. These findings seem to indicate that there are clear advantages to subareolar injection for SLN localization. It avoids the need for image-guided injection in instances of non-palpable lesions, and of overlap of the diffusion zone in lesions in the upper outer quadrant with that of the SLN in the axilla, and in medial lesions with internal mammary lymph nodes. Subareolar injection may also allow the use of the SLN biopsy technique in patients with multicentric breast cancer[54].

There is undoubtedly communication between breast and dermal lymphatics, and the lymphatic channels are much richer at the subcutaneous level than at the peritumoural site. Administration of a radioisotope tracer at subdermal or subareolar sites is supposed to enhance the SLN identification rate; subdermal injection over the primary tumour and subareolar injection are becoming increasingly popular techniques. However, it remains unclear whether the subdermal, subareolar and parenchymal lymphatics of the breast always drain into the same nodes and which route best simulates the spread of breast cancer[1,12,48,56–59]. Roumen *et al.*[58] pointed out that peritumoural and intradermal injections produce a small number of sequential mismatches for 'hot spots' in the axillary region. In particular, a so-called 'regional mismatch' was seen in nine (14 per cent) of 66 relating to the internal mammary nodes in their study.

It is important to realize that the intradermal injection route is apparently unable to detect a SLN in the parasternal/internal mammary region[4,58,60,61], while internal mammary SLNs can be visualized after a peritumoural injection[21,46,53]. In a study by Roumen *et al.*[53] parasternal drainage was visualized by means of peritumoural injection in nine (14 per cent) of 66 positive lymphoscintigraphy cases (in two patients the internal mammary chain was the only location). In another study by Roumen *et al.*[58], however, internal mammary nodes visualized after peritumoural injection could not be visualized with the intradermal technique. Similarly, in a study by Leong *et al.*[46] no internal mammary nodes were seen in any of 50 patients following intradermal injection, whereas six of 35 patients with peritumoural injections had internal mammary lymph nodes identified. Although subdermal and intradermal injections can help to visualize the superficial lymphatic system running towards the axilla, they do not do this for the deep lymphatic system running to the internal mammary, interpectoral or intramammary nodes[59].

Peritumoural injection and subdermal, intradermal or subareolar injection may complement each other, resulting in enhanced success rates. If internal mammary, interpectoral or intramammary lymph nodes are not targeted for SLN biopsy, the use of peritumoural injection of blue dye and either subdermal or subareolar injection of radioisotopes can maximize the identification of axillary SLNs[45]. Intradermal or subareolar injection requires only a small radioisotope dose, which results in lower counts at the injection site and less interference from the 'blast' zone, thus allowing a more precise use of radiolocalization in the axilla[62]. If internal mammary, interpectoral or intramammary lymph nodes are included as biopsy targets, however, the peritumoural injection of a radioisotope combined with the intradermal para-areolar injection of blue dye may be the best choice[58]. In particular, peritumoural injection maximizes detection of internal mammary SLNs with radioisotope. This cannot be done with blue dye, although intradermal injection of blue dye is effective for identifying axillary SLNs. Further study is required to assess the optimal injection sites for blue dye and radioisotopes.

Lymphoscintigraphy *versus* hand-held γ probe

Lymphoscintigraphy may help to identify lymphatic channels and lymph nodes, and to define unpredictable nodal draining basins. It is well established in lymphatic mapping for melanoma, where it identifies anomalous patterns of lymphatic drainage and so has a direct effect on the surgical approach. However, the efficacy of preoperative lymphoscintigraphy remains controversial in breast cancer. Its main advantage is that it allows accurate preoperative localization of the SLN and thereby minimizes the extent of dissection[21,36,39,53]. Several investigators have been able to visualize SLNs in 75–98 per cent of patients by means of lymphoscintigraphy[4,21,38,39,53]. In a study by Kollias *et al.*[63] the SLN was identified in 113 (97 per cent) of 116 patients with positive lymphoscintigraphic findings, but in only 29 (55 per cent) of 53 patients with negative findings. Noguchi *et al.*[35] used a γ probe to identify the SLN successfully in all patients with a 'hot spot' visualized by lymphoscintigraphy. Thus, a positive lymphoscintigram is an important factor associated with successful intraoperative mapping, while a negative lymphoscintigram does not preclude successful radiolocalization at surgery[16,35,64,65].

Recently, however, Burak *et al.*[64] and McMasters *et al.*[65] have demonstrated that preoperative lymphoscintigraphy offers no advantage with respect to SLN localization or false-negative rate compared with management without lymphoscintigraphy. With a hand-held γ probe and using intraoperative mapping, axillary SLNs can be spotted in the operating room even though they cannot be visualized with lymphoscintigraphy[16,35,64,65]. These investigators consider intraoperative scanning with the hand-held γ probe to represent the essence of the isotope technique, but in their studies none of the tumours showed drainage to the internal mammary lymph node chain on lymphoscintigraphy.

Probably, then, lymphoscintigraphy is most useful in delineating the lymphatic drainage pattern to internal mammary lymph nodes, allowing appropriate clinical decisions to be made. Although blue dye does not allow visualization of the internal mammary lymph nodes, a SLN may be visualized in the internal mammary chain when preoperative lymphoscintigraphy is performed[36,38,53]. Noguchi *et al.*[35] found that the internal mammary SLN could be visualized by means of lymphoscintigraphy, but not with the γ detection probe. These nodes might, therefore, be overlooked if not detected by lymphoscintigraphy[48]. Arguments have been made in favour of lymphoscintigraphy providing a 'road map' for surgeons. So it can be said that most studies suggest that preoperative lymphoscintigraphy yields valuable information on the anatomical site of the SLN and the level at which it is located; in some rare instances it will also show other areas of lymphatic drainage, such as the internal mammary chain[35,36,38,53,66]. The author's preference for SLN identification involves a triple technique, comprising preoperative lymphoscintigraphy combined with γ probe-guided and dye-guided methods.

Relevance and identification of internal mammary sentinel lymph nodes

The SLN is most commonly located in the axilla, but it may also be located in the internal mammary chain or elsewhere[5]. The clinical relevance of internal mammary SLN biopsy is a matter of debate. Some investigators do not believe that a lack of internal mammary node imaging is of clinical relevance, because internal mammary dissection has largely been abandoned[67,68], but others believe that internal mammary SLNs are clinically relevant because they have the same prognostic significance as axillary nodal metastases[69,70]. Internal mammary lymph node metastases occur in 7–15 per cent of axillary node-negative and 30–50 per cent of axillary node-positive patients, and this may have important implications for decision making about internal mammary radiotherapy and adjuvant chemotherapy[71,72]. There is also renewed interest in chest wall irradiation in axillary node-positive patients who have had a mastectomy because of a possible improvement in survival[73,74].

Blue dye is not capable of identifying SLNs outside the axilla. Noguchi *et al.*[75] reported that the dissection of blue-stained lymphatic vessels and nodes in the internal mammary chain could be difficult after resection of the primary tumour because the blue dye travels rapidly through the lymphatic vessels, and may not remain in the internal mammary lymph nodes long enough for surgical identification and excision.

Internal mammary SLNs can be identified by lymphoscintigraphy and/or the γ probe-guided method. Using lymphoscintigraphy, Uren *et al.*[38] reported unexpected drainage across the centre line of the breast to either the axillary lymph nodes or internal mammary lymph nodes in 32 per cent of patients with inner or outer quadrant lesions, with nine of the 34 patients having an SLN in the internal mammary chain. Other authors have also used lymphoscintigraphy to identify internal mammary SLNs[21,36,40,46,47,53,75,76]. A hand-held γ probe, on the other hand, has enabled several investigators to find and excise internal mammary SLNs[30,39,40,47]. Harlow *et al.*[47] found extra-axillary 'hot spots' in 44 (6 per cent) of 680 patients. These extra-axillary SLNs were located in the internal mammary lymph nodes in 34 of the 44 patients, while extra-axillary involvement was confirmed histologically in only three of them. In a study by Winchester *et al.*[40] internal mammary SLNs were identified by radioactive localization in 20 (11 per cent) of 180 patients, with three patients in the cohort having histologically proven metastases to internal mammary lymph nodes.

However, the presence of very small lymph nodes in the internal mammary chain of patients with breast cancer has been recognized by pathologists after internal mammary lymph node dissection[77]. Neither lymphoscintigraphy or a γ probe would be able to detect the limited accumulation of isotopes in these nodes. Furthermore, the obliteration of regional nodes by gross tumour involvement may adversely affect both the localization rate and the predictive value of SLN biopsy[27]. Nodes with major tumour deposits often have very low uptake in the area of the tumour, whereas high counts are noted in the remaining intact nodal architecture.

Internal mammary SLN biopsy, therefore, seems to be relevant and a small but increasing number of institutions remove internal mammary SLNs for analysis[40,47,75,78]. However, identification of internal mammary SLNs is still in the experimental stage. The metastatic rate of internal mammary SLNs reported in some studies is still lower than expected[40,47]. Further study is thus required to assess the role of SLN biopsy of the internal mammary nodes. As described previously, the peritumoural injection of a radioisotope combined with the intradermal para-areolar injection of blue dye would be indicated[58]. It has been recommended that surgeons in the process of learning internal mammary SLN biopsy should also perform a back-up internal mammary lymph node biopsy[12,75]. A biopsy of the first and second intercostal spaces would provide accurate information on internal mammary nodal status. A technique of internal mammary lymph node biopsy has been described in detail elsewhere[47].

Diagnosis of sentinel lymph node metastases

Histological examination: step sectioning with haematoxylin and eosin staining combined with immunohistochemical staining

The gold standard for the assessment of axillary lymph nodes in patients with breast cancer is represented by haematoxylin and eosin (HE) staining of paraffin sections. However, the likelihood of detection of micrometastases by routine histological examination of the SLN is limited. To avoid false-negative evaluations, step sectioning[79–81] with the addition of immunohistochemical (IHC) staining[7,10,82–85] makes a more intensive pathological examination feasible. With these techniques, SLN biopsy allows the pathologist to focus on a small number of lymph nodes most likely to contain tumours.

The incidence of micrometastases detected by serial or step sections and cytokeratin IHC staining is reported to be approximately 20 per cent in dissected axillary lymph node specimens considered tumour negative at standard pathological examination[7,10,79,82–85]. Giuliano *et al.*[10] reported that 26 of 68 tumour-involved SLNs had micrometastases only, 11 of which were identified by IHC staining for cytokeratin, but not by HE examination. They also clearly demonstrated the efficacy of enhanced pathological examination of the SLN in breast cancer. Their yield of positive axillary nodes increased from 29 per cent (in 134 patients who underwent ALND with conventional pathology) to 42 per cent (in 162 patients of comparable stage who underwent SLN biopsy with enhanced pathology). There is, therefore, no question that the influence of upstaging by enhanced pathological examination of the SLN will improve the therapeutic results at each stage (the Will Rogers effect).

However, the optimal number of HE and immunohistochemically stained sections to be examined in practice has not yet been determined. Controversy remains as to the minimal amount of histopathological evidence that needs to be obtained from the SLN. Turner *et al.*[82] have recommended obtaining permanent sections from at least two levels of the tissue block at 0·04-mm intervals for HE staining and cytokeratin IHC staining. This represents eight sections of a bisected lymph node. The additional step sectioning with IHC staining did not significantly increase the number of patients identified with tumour-positive SLNs in their study. However, Jannink *et al.*[81] considered that serial sectioning at 0·5-mm intervals with HE and IHC staining is appropriate and cost effective; in this series, the average number of SLNs examined per case was 2·6 and the average number of sections per node was 14, resulting in 36 sections (2·6 × 14) per case for review.

In a study by Dowlatshahi *et al.*[86], on the other hand, tumour metastases were found in only six patients (12 per cent) when the SLNs were sectioned at 2-mm intervals and stained with HE, compared with 30 patients (58 per cent) when the same lymph nodes were serially sectioned at 0·25-mm intervals and stained with cytokeratin. Of 24 patients whose metastases were detected by means of serial sectioning and cytokeratin staining, 12 had isolated tumour cells and 12 had colonies of malignant cells. The authors suggested that most significant metastases will be found with cytokeratin staining at intervals of 0·25 mm thickness. Because the average maximum dimension of a malignant ductal cell is 0·02 mm, a colony of over 20–30 cells is likely to be detected on sections made at these intervals. This should be proposed as a minimum standard. To section the SLN in this fashion, however, requires 40 sections for an SLN measuring 1 cm in diameter.

Currently, an increasing number of investigators performing SLN biopsy for breast cancer rely on serial sectioning of the SLN, with both HE and IHC staining of each section. However, the large number of sections cut, sectioned and reviewed for SLN requires greater involvement of the technologist and the pathologist, and IHC staining is more expensive than HE staining. In a study by Noguchi *et al.*[33] the addition of IHC staining did not significantly improve the detection of axillary lymph node metastases. Further work is therefore needed to enable a consensus to be reached on the most sensitive and cost-effective technique for pathological examination of the SLN for the staging of breast carcinoma.

Intraoperative examination using frozen section and/or imprint cytology

Immediate and reliable intraoperative information regarding the status of the SLN would be useful as it would enable a decision to be made whether or not to perform complete ALND at the time of the initial operation. Several investigators have examined the value of frozen section and imprint cytology for the intraoperative assessment of SLNs.

Haematoxylin and eosin staining of frozen section

The accuracy of SLN diagnosis using frozen section has been questioned in several studies[4,15,29,87,88]. The sensitivity range for frozen-section examination of the SLN is only 64–74 per cent. Veronesi *et al.*[4] reported a sensitivity of 64 per cent, with a false-negative intraoperative diagnosis in 17 per cent of cases. In a large series[29] the same authors reported a false-negative rate of 32 per cent for frozen-section evaluation of the SLN, which makes the approach inappropriate for deciding whether or not to perform a complete ALND[84].

Recently, however, the reliability of intraoperative examination of SLN using frozen sections has improved[35,89]. Viale *et al.*[89] sectioned frozen SLNs subserially at 0·05-mm intervals. For each SLN, one section was stained with HE and the other was immunostained for cytokeratins using a rapid IHC assay, resulting in an overall accuracy of 97 per cent, with a sensitivity of 93 per cent and a specificity of 100 per cent. It was concluded that extensive intraoperative examination of SLNs by frozen-section examination could attain a sensitivity comparable to that obtained by routine histological examination without intraoperative frozen section.

Cytological examination (imprint cytology)

Examination by imprint cytology may be useful for determining the status of the SLNs during surgery, because multiple cut surfaces can be examined quickly with this technique[87,90]. It would be of interest to evaluate whether imprint cytology can be used as an alternative technique when it is not possible to use frozen section, or whether it has enhancement value when combined with frozen section[79,91].

Van Diest *et al.*[91] halved SLNs less than 10 mm in diameter and laminated SLNs of 10 mm or more in diameter into pieces 5 mm in size. Imprints were then made of all cut surfaces and stained. This resulted in a sensitivity of 62 per cent and a specificity of 100 per cent. The diagnostic accuracy of imprint cytology of SLNs did not exceed that of frozen-section examination in this study. Ratanawichitrasin *et al.*[92], however, divided SLNs in two if the diameter was less than 8 mm, or cut them into multiple sections 3 mm thick if the diameter was greater than 8 mm. They reported a sensitivity of 82 per cent and a specificity of 100 per cent for determining the status of the SLN by imprint cytology. Motomura *et al.*[93] serially sectioned SLNs at 2-mm intervals if they were 4 mm or greater in diameter, or bisected if they were smaller than 4 mm. They reported a sensitivity of 91 per cent and a specificity of 99 per cent, although the results of imprint cytology were compared only with those of IHC examination of SLNs. However, imprint cytology requires an experienced surgical cytopathologist to evaluate the specimen and interpret the findings. In most institutions, therefore, imprint cytology of SLNs may not be suitable as a final staging procedure and must be complemented by histology[94]. Evidence to date suggests that intraoperative cytological examination should be employed in conjunction with frozen-section examination.

The accuracy of SLN diagnosis by frozen section[35,89] as well as by imprint cytology[90,92,93] improves with an increase in the number of sections. This allows the 25–30 per cent of patients who have positive nodes to undergo a completion ALND under the same anaesthetic and thus avoid a second procedure[95]. However, it is highly likely that even such intraoperative examination of frozen sections and/or imprint cytology would fail to detect micrometastases consisting of a single cell or a small group of malignant cells in SLNs. An ongoing randomized prospective trial[96] will answer the question whether residual disease will increase axillary relapse.

Reverse transcriptase–polymerase chain reaction analysis

Reverse transcriptase polymerase chain reaction (RT–PCR) analysis is receiving increasing attention as an ultrasensitive technique for the detection of occult metastases[97]. Recently, some investigators have examined SLNs by using RT–PCR for carcinoembryonic antigen (CEA) and mammoglobin analysis, and have reported an improvement in the sensitivity of SLN biopsy[98]. Kataoka *et al.*[98] found CEA to be expressed in 25 per cent of 48 patients with HE-negative SLNs, and mammoglobin expressed in 21 per cent. While HE staining of SLNs could predict axillary lymph node status with an accuracy of 95 per cent and a false-negative rate of 6 per cent, RT–PCR improved these to 99 and 3 per cent respectively. They concluded that SLN diagnosis using RT–PCR is a powerful and sensitive method.

Unlike melanoma, for which the tyrosinase marker has clearly been identified as specific and reliable for the detection of micrometastases, there is as yet no clearly defined RT–PCR marker or set of markers for breast cancer[99]. Moreover, the prognostic significance of micrometastases detected with this new technique and of tumour markers has not been determined[99,100]. The usefulness of this technique, which can detect one malignant cell in one million lymphocytes[96], two orders of magnitude greater than that obtained with HE staining, requires further evaluation because the test may be too sensitive to be clinically useful[79,81,101]. It seems unlikely that the majority of such malignant cells would escape immune surveillance and acquire the traits necessary to become clinically important. The RT–PCR method, therefore, has the potential to improve the sensitivity of SLN biopsy, but requires further study[102].

Significance of micrometastasis in sentinel lymph nodes

The clinical significance of micrometastatic disease has remained controversial. Some authors question the significance of these metastatic deposits, but most series (especially those with longer follow-up) indicate that the presence of these tiny metastases has implications for disease-free and overall survival[71,103]. In a review of the literature, Dowlatshahi *et al.*[71] found that all eight studies, using serial sectioning and HE and/or IHC staining for more than 100 patients and published after 1982, demonstrated an association between micrometastases and poor outcome.

Nevertheless, it is unlikely that all tumour cells detected in lymph nodes are clinically significant. Although the distinction between micrometastases (smaller than 2 mm) and macrometastases (larger than 2 mm) in axillary nodes is a quantitative rather than a qualitative difference, the survival of patients depends more on the quantity of lymph node metastases than on their quality. For example, prognosis is directly related to the number of positive axillary lymph nodes. It has been suggested that colonies of cells are clinically significant and that individual cells generally are not[86] so that subclassification of micrometastasis in breast cancer may be required[104].

On the other hand, an overview study has shown that 38–67 per cent of patients with breast cancer and positive SLNs have no disease in other (non-sentinel) nodes[16]. This finding not only strongly supports the SLN concept, but also suggests that ALND can be avoided in such patients. Several investigators[83,105,106] have sought to identify factors that might predict which patients with positive SLNs are at a low risk of having disease-harbouring non-sentinel nodes. They found that tumour cells are unlikely to be found in the latter if the primary breast tumour is small and SLN involvement is micrometastatic.

So it may be possible to treat patients with T_1 tumours and micrometastasis in the SLN with SLN biopsy only, making full ALND unnecessary for these patients[83]. In other words ALND can be avoided in these patients, even assuming that histological examination of the SLN may fail to detect micrometastases. It is, therefore more important to diagnose a colony of malignant cells in the SLN rather than a cell or a small group (less than ten) of malignant cells in a lymph node.

Elimination of axillary lymph node dissection as a result of sentinel lymph node biopsy

The growing demand from patients for less invasive procedures has created considerable incentives for accepting SLN biopsy without ALND as standard practice. In a trial sponsored by the American College of Surgeons[96], each institution's principal investigator is required to document a 90 per cent accuracy rate and a 90 per cent staging accuracy in at least 30 consecutive cases of SLN biopsy followed by complete ALND. When planning the elimination of ALND as a result of SLN biopsy in clinical practice, however, one must estimate the actual risks and consequences of allowing residual disease to remain in the axilla. Several studies have demonstrated that SLN biopsy is highly accurate and sensitive in patients with small tumours, and there have been no reports of false-negative SLN biopsy for breast cancer less than 1·0–1·5 cm in size[4,15,21,107]. The high accuracy of SLN biopsy for patients with small tumours is in part due to the low probability of axillary metastases. It is, therefore, reasonable in actual practice to offer the option of no ALND to patients with small breast cancers (tumour size smaller than 1·5 cm or T_1) and a negative SLN. This strategy is supported by findings, already described, that tumour cells are unlikely to occur in non-sentinel nodes if the primary breast tumour is small and SLN involvement is micrometastatic[83,105,106]. SLN biopsy without ALND may be also applied to cases of extensive and/or high-grade (comedo subtype) duct carcinoma *in situ*[108].

However, recent studies have demonstrated that SLN biopsy is as accurate for the assessment of the axilla in patients with T_2 tumours as it is for those with T_1 tumours[109,110]. Bedrosian *et al.*[109] reported that SLN biopsy can be applied to large tumours (larger than 2 cm but smaller than 5 cm) with a 99 per cent SLN identification rate and a false-negative rate of 3 per cent. Of 30 SLN-positive patients with tumours larger than 3 cm, only three of eight patients with micrometastasis (less than 2 mm) to the SLN had positive non-sentinel nodes compared with 21 of 22 with macrometastasis (larger than 2 mm). This excellent result was achieved by extensive histological examination with IHC staining. A false-negative rate of no more than 5 per cent seems reasonable for performing SLN biopsy without ALND.

Because histological examination of the SLN still has its limitations, it is highly unlikely that all false-negative cases can be eliminated. In particular, intraoperative diagnosis by either frozen-section examination or imprint cytology is unlikely to identify micrometastases. Moreover, it is not clear whether the residual nodal disease, particularly in patients with larger invasive tumours (larger than 2 cm but smaller than 5 cm) undergoing SLN biopsy without complete ALND, will significantly increase the axillary lymph node recurrence rate. This risk is all the more a matter of concern because of the therapeutic benefits of axillary radiation therapy and systemic chemotherapy that may eradicate most micrometastases and some macrometastases[111]. These important questions can only be answered by a randomized prospective trial[96]. Such a trial addressing these issues is being conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP B-32). SLN biopsy alone will be compared with SLN biopsy followed by ALND.

Currently, several surgeons on the basis of their experience with SLN biopsy have already abandoned routine ALND for patients with $T_{1\text{-}2}$ N_0 disease and a negative SLN biopsy result[18,19,112–114]. However, subsequent relapse in the regional nodal basin should be similar to that after a conventional ALND (less than 1 per cent)[115], while it has not yet been reported in the published literature. In practice, ALND can be avoided in patients with small tumours (T_1) who have a negative SLN[12,15]. However, elimination of ALND in those with large tumours (T_2) who have a negative SLN should be considered only by surgeons highly experienced in SLN biopsy who have access to a pathologist experienced in performing an intensive histological examination of SLNs. In most institutions, therefore, it is recommended that SLN biopsy with back-up

ALND should be used for most T_2 cancers until the results of the aforementioned clinical trial are available.

Conclusion

1 Although the SLN can be identified successfully by experienced practitioners using either the dye-guided or γ probe-guided method, identification is facilitated when both techniques are used together.
2 The use of medium particle radioisotope tracers (particle size 200–1000 nm) is preferable, because the SLN identification rate is relatively high and only one or two SLNs can be identified even the day after injection.
3 A smaller radioisotope dose (0·2–0·3 mCi) is more effective because it reduces the 'shine through' effect from the high level of radioactivity at the tumour site. On the other hand, while a smaller volume of tracer might be adequate to identify SLNs when administered with subdermal or subareolar injection, a larger volume may be necessary for peritumoural injection.
4 The subdermal or subareolar injection technique has attractive practical features, but there is currently insufficient evidence that drainage of tracer injected anywhere in or underneath the skin of the breast reflects drainage from the cancer. Peritumoural injection and subdermal, intradermal or subareolar injection may complement each other, thereby increasing success rates. If internal mammary lymph nodes are targeted for SLN biopsy, peritumoural injection maximizes detection with radioisotopes of internal mammary nodes.
5 Preoperative lymphoscintigraphy yields valuable information on the anatomical site of the SLN and the level at which it is located; in some rare instances it will also show other areas of lymphatic drainage such as the internal mammary chain.
6 Identification of internal mammary SLNs remains controversial. Further study is required to assess the role of SLN biopsy of the internal mammary nodes. It is recommended that surgeons who are learning internal mammary SLN biopsy should perform a back-up internal mammary lymph node biopsy.
7 To increase the chance of finding metastases in the SLN, step sectioning combined with HE and IHC staining of permanent sections is desirable. However, further studies are needed to reach a consensus on the most sensitive and cost-effective technique for pathological examination of the SLN for the staging of breast carcinoma.
8 Extensive intraoperative examination of SLNs using frozen section and imprint cytology could attain a sensitivity similar to that obtained by histological examination of permanent sections. However, imprint cytology requires an experienced surgical cytopathologist to evaluate the specimen and interpret the findings.
9 It is highly unlikely that all false-negative cases can be eliminated even by detailed histological and cytological examination of the SLN. Nevertheless, patients with T_1 tumours with micrometastases in the SLN have shown no evidence of tumour in the non-sentinel nodes. In other words, ALND can be avoided for these patients, even assuming that the histological examination of the SLN may fail to detect micrometastases.
10 The role of RT–PCR for SLN analysis in breast cancer remains under investigation; it may be too sensitive to be clinically useful.
11 In practice, routine ALND can be avoided in patients with T_1 tumours when the identified SLN proves to be histologically negative. However, investigation of long-term regional controls and of survival in a prospective randomized trial is necessary before SLN biopsy can be expected to replace routine ALND, particularly for patients with T_2 tumours.

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Randomized clinical trial of laparoscopic *versus* open abdominal rectopexy for rectal prolapse

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Background: The objectives of this study were to compare both subjective clinical outcomes and the objective stress response of laparoscopic and open abdominal rectopexy in patients with full-thickness rectal prolapse. Abdominal rectopexy for patients with rectal prolapse is well suited for a laparoscopic approach as no resection or anastomosis is necessary.

Methods: Forty patients with a full-thickness rectal prolapse were randomized before operation to a laparoscopic group and an open group. They agreed to conform to a clinical pathway (CP) of liquid diet (CP1) and full mobility (CP2) on day 1, solid diet (CP3) on day 2 and discharge (CP4) before day 5. Their compliance was monitored by an assessor blinded to the operative group, who also rated pain and mobility. Patient-controlled morphine use was documented. Neuroendocrine and immune stress response and respiratory function were measured.

Results: Some 75 per cent of all clinical pathway objectives of early recovery were achieved in the laparoscopic group compared with 37 per cent in the open group ($P < 0.01$). Significant differences in favour of laparoscopy were noted with regard to narcotic requirements, and pain and mobility scores. Differences in objective measures of stress response favouring laparoscopy were found for urinary catecholamines, interleukin 6, serum cortisol and C-reactive protein. No differences were noted in respiratory function but significant respiratory morbidity was greater in the open group ($P < 0.05$). None of the measured outcomes, subjective or objective, favoured the open group apart from operating time, which was significantly shorter (153 *versus* 102 min; $P < 0.01$).

Conclusion: This study has demonstrated significant subjective and objective differences in favour of a laparoscopic technique for abdominal rectopexy. The advantages were all short term but no evidence of any adverse effect on longer-term outcomes was observed.

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Introduction

Laparoscopic surgery has been used over the past decade with resection of the colon and rectum for benign and malignant conditions. The technical limitations of specimen retrieval and bowel anastomosis, and port-site recurrence in cancer surgery have limited the impact of laparoscopy on colorectal surgery. This is despite numerous early case studies and small randomized controlled trials combined with ongoing multicentre trials[1,2]. Full-thickness rectal prolapse repaired by fixation rectopexy is well suited to a minimally invasive laparoscopic approach as no specimen is removed and no anastomosis is necessary[3–7]. An initial historical controlled trial suggested that laparoscopic rectopexy was superior to open rectopexy with respect to pain and return to normal physiological function[3].

The objectives of this study were to determine whether a laparoscopic approach to rectopexy has advantages over the traditional open approach in either subjective clinical outcome or objective stress response. The study was designed to assess large differences in perioperative outcomes (using a small sample size with good internal validity and standardization of therapy) rather than any small differences in longer-term outcomes such as recurrent prolapse, postoperative constipation and faecal incontinence. To assess these endpoints adequately would require a multicentre study (difficult in terms of feasibility, poor internal but good external validity)[8]. Differences in event rates with respect to these were assessed in the present study but no differences were detected since the commencement of laparoscopic rectopexy in 1994.

Patients and methods

From December 1996 to December 1999 all patients with full-thickness rectal prolapse with or without faecal incontinence referred to one teaching hospital department of colorectal surgery were assessed for eligibility. Patients were excluded if concomitant gynaecological procedures were planned, rectopexy had been performed previously or a large irreducible prolapse was present which would be better repaired by perineal proctosigmoidectomy. Patients with obstructive defaecation and concomitant rectocele or anal mucosal prolapse were offered a Delorme procedure. Patients with intractable constipation preceding the development of the rectal prolapse were advised to have a resection rectopexy. Constipation developing in conjunction with the rectal prolapse was not an exclusion criterion nor was previous lower abdominal surgery. Institutional ethics committee approval was obtained for this trial.

The surgical technique has been described previously; however, modifications in the staple driver, and improvement in bowel grasping forceps and surgical technique have reduced the size and number of operating ports from five to three[3]. Standardization of the surgical technique was agreed and achieved largely as 85 per cent of enrolled patients were under the care of one surgeon (M.J.S.). Full rectal mobilization to the anorectal junction was performed with a posterior incomplete mesh wrap. The mesh was secured to the sacral promontory with a single spiked chromium staple (12–8720; Smith & Nephew Richards, Memphis, Tennessee, USA). The mesh was secured to the lateral rectum using hernia staples[3].

Subjective clinical outcomes

Patients entering the trial agreed to a standardized clinical pathway (CP) to minimize patient or surgeon bias in favour of either group. The clinical pathway had four subjective outcomes (CP1–4) per patient that were documented by a blinded assessor. They included oral fluids (CP1) and full mobilization (CP2) on day 1 and, if tolerated, a light diet (CP3) on day 2. The patients themselves determined the outcome variables, not the clinicians. The urinary catheter was left in for 48 h to measure total catecholamine excretion and removed on the morning of day 3. Patients were advised that they would be discharged after day 3 but before the end of day 5 (CP4). A specific clinical reason was required for discharge after this date.

Patients were assessed by three gastrointestinal clinical nurse specialists who were trained to assess the trial outcomes before the trial and were independent of the colorectal ward. The assessors were blinded to the operative procedure and the patient was instructed not to inform the assessors. To enhance blinding the clinical notes were marked only as 'laparoscopic rectopexy trial patients'. Patients were assessed by the blinded assessor before operation, at 4, 24 and 48 h after operation, and then daily until discharge. Visual analogue scales for pain and mobility, patient-controlled morphine requirements[9–11], respiratory function[12], oral intake and morbidity were assessed at each visit and blood samples were taken.

Objective outcomes

Twenty-four-hour urine collections were performed to measure catecholamine excretion (adrenaline and noradrenaline)[13]. Preadmission serum tests were performed for fasting cortisol, interleukin 6, C-reactive protein and erythrocyte sedimentation rate (ESR)[13–15]. These were repeated 4, 24 and 48 h after operation. Serum cortisol and interleukin 6 are representative of the acute-phase response (4–24 h), and ESR and C-reactive protein of a delayed stress response (48 h). The respiratory function tests comprised measurement of forced expired volume, vital capacity, and inspiratory and expiratory wedge pressures[12]. The latter two tests best assess the ventilation of the lung bases. The results were measured as change from the individual patient's preoperative values.

Theatre utilization times were measured prospectively by the research assistant. Two measurements were made: the time from entering the anaesthetic bay to leaving the theatre and the time from the first incision to the last stitch. The 30-day morbidity and mortality rates were recorded prospectively for both groups by the blinded assessor. All potential morbidities (for example fever) were documented. A final determination and definition of morbidities was performed at the conclusion of the study by a panel of clinicians blinded to the operative group. Morbidities were classified as all documented events (for example fever unknown cause), all definable morbidities (for example urinary tract infection) and major morbidities (defined as those requiring active intervention and delaying discharge, such as pulmonary oedema and pneumonia).

Statistical analysis

Statistical analysis was performed by a statistician to whom the operative group was identified only as group A or B. Unblinding was performed only after completion of all analyses. Analysis was performed using the Wilcoxon rank sum test, the Student t test for continuous variables, and χ^2 test and Fisher's exact test (less than five in one or more cells) for proportions. Sample size calculations were based on the power to detect only clinically significant differences of subjective outcomes (i.e. proportions ranging from 20 to 40 per cent, $\alpha = 0{\cdot}05$, $\beta = 0{\cdot}80$, sample size 17–24 in each group)[16].

Results

Of 101 patients with a full-thickness rectal prolapse seen during the accrual of the study, 40 were randomized to the trial. Only three patients deemed by the surgeon to be suitable for rectopexy refused the trial. Of the 40 patients, one patient referred from an outside institution who was randomized to open rectopexy then refused any surgery and was excluded from the analysis. One patient with a full understanding of the randomization process refused open surgery after randomization into this group. The trial management committee met and elected to perform a laparoscopic rectopexy and include the clinical data in the open group (intention-to-treat analysis).

Thus 39 of the 40 patients randomized completed the trial. No patient required intraoperative conversion from a laparoscopic to an open procedure. There were no significant differences in duration of prolapse, previous abdominal surgery, age, gender, duration or severity of incontinence, or preoperative constipation scores in the two cohorts. The mean total operating room time and surgical time were just over 50 min longer for the laparoscopic group ($P < 0{\cdot}01$) (*Table 1*). The mean day of discharge following operation was significantly earlier in the laparoscopic group (3·9 *versus* 6·6; $P < 0{\cdot}01$). After a mean follow-up of 24 months there has been one recurrence in the open group and none in the laparoscopic group.

In the laparoscopic group 75 per cent of the clinical objectives of early recovery (CP1–4) were fulfilled compared with only 37 per cent in the open group (60 of 80 *versus* 28 of 76; $P < 0{\cdot}01$) (*Table 2*). Nineteen of 20 patients in the laparoscopic group were discharged by day 5 compared with nine of 19 in the open group ($P < 0{\cdot}01$). Sixteen patients in the laparoscopic group tolerated solid diet by day 2 compared with only three in the open group ($P < 0{\cdot}01$), even though both were offered fluids and diet at the same time. More patients in the laparoscopic group tolerated fluids on day 1 (17 of 20 *versus* 12 of 19) and were fully mobile on the first postoperative day (eight of 20 *versus* four of 19) but these results were not statistically different.

The objective measures of stress response to surgery all favoured the laparoscopic group. The haemoglobin level at 48 h had fallen more in the open group (1·2 *versus* 1·9 g per cent; $P = 0{\cdot}02$). The increase in the acute-phase reactant interleukin 6 was greater but not significantly different in the open group at 4 h (11 *versus* 111 pg/ml) and 24 h (21 *versus* 44 pg/ml), and equivalent at 48 h (13 *versus* 12 pg/ml). The increase in serum cortisol was significantly greater in the open group at 4 h (343 *versus* 582 nmol/l; $P = 0{\cdot}03$), 24 h (79 *versus* 387 nmol/l; $P < 0{\cdot}01$) and at 48 h (24 *versus* 437 nmol/l; $P = 0{\cdot}03$). Similarly, significant differences were found in C-reactive protein at 24 h (44 *versus* 77 mg/l; $P = 0{\cdot}03$) and 48 h (70 *versus* 112 mg/ml; $P = 0{\cdot}05$) favouring the laparoscopic group. There were no significant differences in ESR at 4, 24 or 48 h.

The amount of catecholamine recovered in the 24-h urine collection was significantly lower in the laparoscopic

Table 2 Clinical pathway subjective outcomes

		Laparoscopic (n = 20)	Open (n = 19)	P
CP1	Clear fluids day 1	17	12	0·11
CP2	Fully mobile day 1	8	4	0·18
CP3	Solid diet day 2	16	3	< 0·01
CP4	Discharge by day 5	19	9	< 0·01
Total		60 of 80 (75)	28 of 76 (37)	< 0·01

Values in parentheses are percentages. CP, clinical pathway

Table 1 Operating times, hospital stay and haemoglin changes

	Laparoscopic	Open	P†
Theatre utilization time (min)	199 (135–255)	148 (95–255)	< 0·01
Surgical operating time (min)	153 (95–215)	102 (59–185)	< 0·01
Mean day of discharge	3·9 (3–6)	6·6 (3–15)	< 0·01
Postoperative haemoglobin drop (g%)*	1·2 (– 0·9 to 3·5)	1·9 (0·3–3·5)	0·02

Values are mean (range). *48 h after operation. †Student's t test

Table 3 Long-term outcomes

	Laparoscopic	Open
Follow-up (months)	23·8 (2–52)	24·5 (2–51)
Recurrence of prolapse	0	1
Incontinence score[17]		
Preoperative	6·6 (0–13)	7·8 (0–13)
Postoperative	1·6 (0–11)*	2·0 (0–9)*
Constipation VAS		
Preoperative	2·4 (0–7·7)	2·4 (0–7·1)
Postoperative	2·9 (0–8·4)	2·4 (0–9·3)

Values are mean (range). VAS, visual analogue scale. $^*P < 0{\cdot}01$ *versus* preoperative score (Student's *t* test and Wilcoxon rank sum test). There were no significant differences between laparoscopic and open groups for any of the variables

group (adrenaline 38·1 *versus* 72·7 nmol/l ($P < 0{\cdot}01$); noradrenaline 118 *versus* 281 nmol/l ($P < 0{\cdot}01$)). No differences were found between the two groups in respiratory function over the first 48 h.

There were significant differences in morbidity between the two groups. All potential adverse events occurred more often in the open group (six of 20 *versus* 14 of 19; $P < 0{\cdot}01$). Defined morbidities (three of 20 *versus* nine of 19; $P = 0{\cdot}03$) and major morbidities (none of 20 *versus* four of 19; $P < 0{\cdot}05$) were significantly fewer in the laparoscopic group. The major morbidities in the open group were cardiorespiratory. The only defined morbidities in the laparoscopic group were atelectasis (one), urine retention (one) and wound infection (one).

Morphine requirements were lower in the laparoscopic group at each of the points of measurement but the differences were not significant. However, the mean(s.d.) total dose of morphine over 5 days was significantly less in the laparoscopic group than in the open group (73(48) *versus* 113(94) mg; $P = 0{\cdot}03$). Significant differences in mean scores in favour of the laparoscopic group were recorded in nine of 16 analogue scores of pain and mobility with trends to significance in a further three (total 12 of 16). All were in favour of the laparoscopic group.

There were significant improvements in continence scores in each group but no differences between the groups (*Table 3*). There was no significant increase in constipation scores in either group and no difference between the groups. The mean visual analogue score for cosmesis was better in the laparoscopic group but not significantly so (0·8 *versus* 2·5; $P = 0{\cdot}10$).

Discussion

This small randomized clinical trial has shown that a rectopexy performed laparoscopically results in less postoperative pain, an earlier return of alimentation and earlier discharge from hospital, at the expense of a longer operation. Blinded assessors and an agreed clinical pathway were used to improve the quality of subjective data. The subjective outcomes in this study coincide with the objective measures of stress response which adds weight to their validity. Apart from operating time there was no subjective or objective measure favouring the open group. That so many results between the two groups were significant with the small sample size suggests a large group difference.

There are no large randomized controlled trials comparing different operations for rectal prolapse and only two published trials have compared laparoscopically assisted colorectal procedures. The first trial, by Milsom *et al.*[1], demonstrated an improved return of bowel function and respiratory function in the laparoscopic group but no decrease in the length of stay (6 *versus* 7 days). They also found a 75-min increase in operating time[1]. The second trial, by Stage *et al.*[2], demonstrated no difference in respiratory function, but decreased pain scores and morphine requirements. They also noted a smaller objective stress response in terms of interleukin 6 and C-reactive protein as well as a significantly shorter length of stay (5 *versus* 8 days), but an increased operating time of 55 min[2]. A third non-randomized controlled trial that assessed interleukin 6 and cortisol stress responses in laparoscopic 'assisted' colorectal resections demonstrated a similar lowering effect of laparoscopy on interleukin but not serum cortisol levels[15].

The data from this randomized controlled trial confirm and augment the differences detected in an original historical controlled trial[3]. With the introduction of a clinical pathway in the current study early alimentation and discharge have improved in both groups compared with the historical controls. None the less there is a relative difference strongly in favour of the laparoscopic group. The difference in operating time has been reduced from 70 min in the previous study to 50 min in the current study. Including this trial, the evidence to date from controlled trials suggests that there is a benefit in terms of the immediate objective stress response but no immediate objective respiratory difference. Combined with the decreased stress response, less ileus, less pain, greater mobility and a decreased morphine requirement, there is less respiratory morbidity and an earlier discharge for patients treated laparoscopically. The increased theatre utilization (50 min) and disposable costs will most likely be offset by both the shorter hospital stay and less need for treatment of minor and major complications. A cost-effectiveness analysis will be the focus of a further evaluation of the data collected from this study.

The limitations of this study include the small numbers of patients and the fact that the technique was performed by one specialized surgical unit and largely by one surgeon. The wide application of the technique still remains to be tested. However, when abdominal rectopexy is chosen as the procedure to correct rectal prolapse, a laparoscopic approach has short-term benefit in terms of return to normal diet and mobility, earlier discharge from hospital and less morbidity. These findings are paralleled by a reduced neuroendocrine and immunological stress response. No long-term differences in constipation, recurrent prolapse or improvement in continence scores between open and laparoscopic approaches have been identified. Interestingly, these data suggest that there was underlying constipation before operation that was not increased significantly by either rectopexy method (*Table 3*). This has brought into question the suggestion from retrospective studies that the major drawback to rectopexy compared with alternative approaches is an increase in constipation.

While long-term studies are required, the data indicate that a laparoscopic technique may be beneficial to patients with rectal prolapse for whom rectopexy is proposed.

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Randomized clinical trial comparing the efficacy of two bandaging regimens in the treatment of venous leg ulcers

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Background: Many venous ulcers are healed by the application of external compression. It has been suggested that bandages capable of producing greater compression enhance healing. The aim of this study was to compare the time to total healing of venous ulcers in two groups of patients treated with different compression regimens in a randomized prospective trial.

Methods: A total of 112 patients was studied and all were treated with a zinc-impregnated paste bandage applied directly to the ulcer. Fifty-seven patients had the paste covered by Tensopress™ and 55 by Elastocrepe™ bandages. Both groups had a tubular bandage applied over the top to retain the bandage in place. All ulcers were stratified and randomized within one of three size groups. The 'venous' aetiology of the ulcer was confirmed on completion by calf pump function tests.

Results: By 26 weeks, 58 per cent of the patients treated with Tensopress™ and 62 per cent of those treated with Elastocrepe™ bandages were healed. The median healing times were 9 and 9·5 weeks respectively. Similar numbers of patients were excluded or withdrawn from both groups. Large ulcers healed significantly more slowly than small ulcers.

Conclusion: There was no significant improvement in venous ulcer healing using higher compression elastic bandages.

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Introduction

Epidemiological studies have estimated the prevalence of active leg ulceration in the UK population to lie between 0·1 and 0·3 per cent[1–4]. About 70 per cent of leg ulcers are caused by venous disease[1,2] and compression bandaging has been used to treat them for centuries[5,6]. 'Elastic compression' was popularized in the UK as a new means of treating ulcers in the 1930s by Dickson-Wright[7]. This approach was supported by Bisgaard in the 1940s[8]. The Unna boot was subsequently used in Scandinavia and the USA; it provided a rigid encasement of the limb which produced compression only when the leg altered its profile during exercise[9]. This type of compression is different from more evenly applied elastic bandaging that should provide constant compression (especially if the leg has an awkward shape). Advocates of inelastic compression claim better results[10,11] and feel that it is safer than elastic compression[12]. All bandages have some elasticity, however, and this has proved difficult to measure *in vivo*. Inelastic, short-stretch bandages have become popular in continental Europe whereas elastic bandages are commonly used in the UK.

In 1992, Callam *et al.*[13] compared two different three-layer bandaging regimens in patients with a venous ulcer. In their study, an 'elastic' regimen was devised using Tensopress™ (Smith and Nephew, Hull, UK), an elasticated two-way stretch Lycra™ bandage (DuPont, Wilmington, Delaware, USA), which was compared with an 'inelastic' system based on Elastocrepe™ Hull, UK, a cotton-elastic bandage (Smith and Nephew). It was found that 54 per cent of ulcers treated with the 'elastic' and 28 per cent of ulcers treated with the 'inelastic' bandages healed within 12 weeks. This difference was statistically significant and it was concluded that the Tensopress™-based 'elastic' bandaging system improved the healing of chronic venous leg ulcers.

The aim of the present study was to compare the efficacy of Tensopress™ and Elastocrepe™ bandages. The bandages were applied over the same paste dressing, with ulcers stratified into three different size categories that have previously been shown to divide patients with ulcers into suitably sized groups[14]. Using a randomized trial, the aim was to confirm whether the greater compression produced by the Tensopress™ bandage improved venous ulcer healing. This design differed from Callam's study in which different retaining bandages were used over each type of compression bandage.

Patients and methods

The study was a prospective, randomized, stratified and open comparison of the bandages used in patients with a venous leg ulcer. The trial protocol was approved by St Thomas' Hospital Ethics Committee. All patients referred to the St Thomas' leg ulcer outpatient clinic were considered for entry into the study. Informed consent was obtained from all participants. Computer-generated tables were used to randomize patients.

Patient assessment

Standard ulcer history and examination forms were completed for each patient on enrolment into the study and the ulcer was photographed. The initial size of the ulcer and the ankle circumference immediately above both malleolli were measured. A full blood count, erythrocyte sedimentation rate, sickle cell test, serum urea, glucose, albumin, rheumatoid factor (Rose–Waaler and latex) and antinuclear factor levels were measured to exclude patients with other conditions that might cause leg ulceration. Human immunodeficiency virus antibody levels were not requested routinely. The resting ankle : brachial Doppler pressure index was also recorded.

Standard ulcer study assessment forms were completed at each subsequent clinic visit. Ulcer size and ankle circumference were recorded at every clinic attendance. Any relevant comments were noted. Photographs were taken at monthly intervals. When it was thought that the ulcer had healed, all scabs were removed and two observers confirmed that the ulcer was healed. A photograph of the healed ulcer was taken and was used to confirm healing by a third party. Complete ulcer healing was defined as the restoration of entirely unbroken skin integrity without any scabs or purulent discharge after removal of all scabs.

Ulcer size stratification

The initial ulcer area was calculated before randomization by multiplying the maximum length and width of the ulcer[15]. Randomization was then stratified by the initial ulcer size into small (0·25–2·5 cm^2), medium (more than 2·5 to 25 cm^2) or large (more than 25 to 100 cm^2).

Exclusion criteria

Exclusion criteria are listed in *Table 1*.

Bandaging regimens

On entry into the study and at each subsequent clinic attendance, standard ulcer dressing techniques were performed by one of a group of seven experienced ulcer clinic nurses. The ulcer and surrounding skin were gently cleaned with saline-soaked cotton wool balls. Three-layer bandages were applied to all patients in a standard manner[16]. The initial turn was placed around the ankle to fix the bandage, which was then taken down over the ankle to compress the foot. The bandage was then taken up over the initial turn to cover the lower leg to knee level using an overlapping figure-of-eight technique[16]. The primary dressing applied directly to the ulcerated area was a Viscopaste™ PB7 bandage (Smith and Nephew). A Tensopress™ or Elastocrepe™ compression bandage was applied next according to the randomization protocol. A Tensoshape™ (Smith and Nephew) graduated cotton-elastic tubular retaining bandage was then applied over the top to prevent slippage. All dressings were left undisturbed until the next clinic visit.

Study withdrawal or completion

Reasons for patient withdrawal from the study or adverse reactions were recorded. Patients could be withdrawn for the reasons shown in *Table 2*.

Patients completed the study if the ulcer healed, or if they had participated in the study for 26 weeks and the ulcer

Table 1 Randomized trial of venous ulcer bandages: exclusion criteria

Significant arterial disease (ankle : brachial pressure index < 0·8)
Diabetes mellitus
Rheumatoid arthritis
Systemic lupus erythematosus
Positive Sickle cell test
Known human immunodeficiency virus infection
Ulcer size < 0·25 cm^2
Ulcer size > 100 cm^2
Known Viscopaste™ sensitivity
Patients receiving drugs that might affect ulcer healing, such as stanozolol, paroven or oxpentifylline
Patients thought not to have a venous ulcer on clinical examination

Table 2 Randomized trial of venous ulcer bandages: possible reasons for patient withdrawal

Adverse reaction to Viscopaste™ or compression bandaging
Non-compliance
Non-attendance or irregular attendance
Patient request
Biopsy-proven malignant transformation

remained unhealed. At this stage a photograph was taken and venous function tests were conducted. Venous duplex imaging, foot volumetry and ascending phlebography were used to evaluate venous anatomy and function. The half-refilling time on foot volumetry was deemed 'abnormal' if it was less than 15 s[17]. Reflux of greater than 0·5 s in the saphenous or popliteal veins was regarded as abnormal if foot volumetry could not be performed. The anatomical status of the deep veins was assessed with ascending phlebography. The number of limbs with post-thrombotic change was recorded. Wherever possible, all three investigations were carried out. A patient was excluded from the study if no objective venous abnormality was detected, even if the ulcer was thought to be venous on clinical examination. An intention-to-treat analysis was also performed on all ulcers included in the study.

Statistical analysis

The outcome measures used were complete ulcer healing, time taken to heal completely and failure to heal within 26 weeks (6 months). An interim data analysis was performed at 12 weeks and a subsequent analysis was performed at 40 weeks to allow comparison with other studies. Outcome was assessed by the Kaplan–Meier life-table analysis. Log rank or χ^2 analysis was also performed where appropriate. Ranges of time to healing were compared with the Mann–Whitney *U* test. Comparison of patients from this trial with others was performed using the Mantel–Haenszel method. The data were processed using desktop calculation, Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA) and the Stata (Stata Corporation, College Station, Texas, USA) and C-Stat (Cherwell Scientific Publishing, Oxford, UK) statistical analysis packages.

Results

Some 112 patients with a venous ulcer were randomized: 57 had Tensopress™ bandages and 55 had Elastocrepe™ bandages applied. Equivalent numbers of ulcers within each size stratification were present in both groups (*Table 3*). Nine patients were excluded from the study following randomization (four Tensopress™ and five Elastocrepe™), and 16 patients were withdrawn during the study (eight in each group) (*Table 4*).

At the end of 26 weeks, 33 patients (58 per cent) in the Tensopress™ group and 34 (62 per cent) in the Elastocrepe™ group had healed (*Fig. 1*). This difference was not statistically significant ($\chi^2 = 0{\cdot}23$, $P = 0{\cdot}623$, log rank test). The mean time to healing was 10 (range 2–23; 95 per cent confidence interval (c.i.) 8 to 12) weeks for the Tensopress™-treated patients, compared with 11 (range 3–25; 95 per cent c.i. 9 to 13) weeks for the Elastocrepe™-treated patients. The median time to healing was 9 and 9·5 weeks respectively. There was no statistically significant difference between the healing times in the two groups ($U = 560{\cdot}5$, Mann–Whitney *U* test).

Table 3 Comparison of ulcer sizes in patients treated with Tensopress™ and Elastocrepe™

	Ulcer size (cm^2)			
	Small (0·25–2·5)	Medium (> 2·5–25)	Large (> 25–100)	Total
Tensopress™	18	23	16	57
Elastocrepe™	17	23	15	55

There was no significant difference in ulcer size distribution between the two groups

Table 4 Reasons for patient exclusion after randomization and withdrawals during the study

	Tensopress™	Elastocrepe™
Exclusions		
Diabetes	3	0
Rheumatoid arthritis	0	2
Systemic lupus erythematosus	1	0
Mixed aetiology	0	1
Human immunodeficiency virus positive	0	1
Squamous cell carcinoma	0	1
Total	4	5
Withdrawals		
Paste allergy	0	1
Bandage skin damage	1	0
Refused treatment	1	0
Non-compliance	0	2
Lost to follow-up	3	3
Incomplete data recorded	3	2
Total	8	8

At 40 weeks, only one further patient had healed in each group (total 34 (60 per cent) of 57 in the Tensopress™ group and 35 (64 per cent) of 55 in the Elastocrepe™ group). This did not affect the statistical significance of the results.

Patients with a large venous ulcer were significantly less likely to heal within 26 weeks than patients with small or medium-sized ulcers (*Fig. 2*) ($\chi^2 = 18{\cdot}05$, $P < 0{\cdot}001$). This effect was not dependent on the type of bandage used (*Table 5*).

Discussion

Multilayer compression bandaging is an effective treatment for venous leg ulceration[18]. In this study, the percentage of

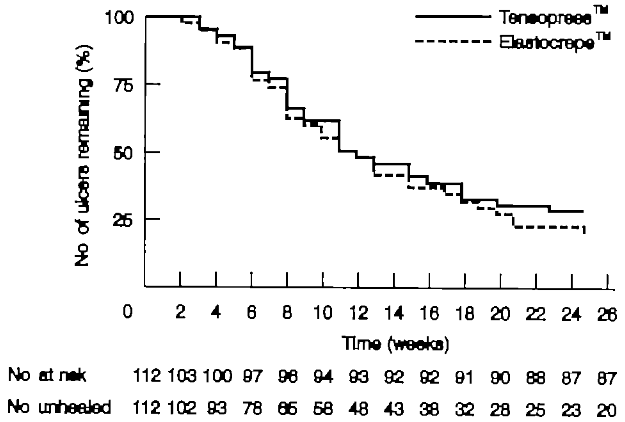

Fig. 1 Kaplan–Meier survival estimates for venous ulcers treated with Tensopress™ or Elastocrepe™ bandages

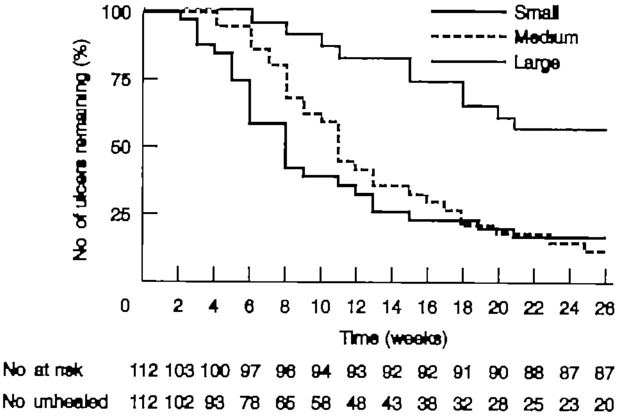

Fig. 2 Kaplan–Meier survival estimates for venous ulcer healing according to size (small, 0·25–2·5 cm^2; medium, >2·5–25 cm^2, large, >25–100 cm^2)

Table 5 Effect of ulcer size on healing

	Tensopress™	Elastocrepe™
Small ulcers healed	13 of 18	13 of 17
Medium ulcers healed	16 of 23	15 of 23
Large ulcers healed	4 of 16	6 of 15
Total	33 of 57	34 of 55

ulcers that healed within 6 months was comparable with other reports[18]. There was no difference between time to healing or percentage of ulcers healed whether Elastocrepe™ or Tensopress™ bandages were applied. This suggests that the differences between the initial properties of the two bandages did not determine whether the ulcers healed. This may not be surprising as compression bandages are left in place for at least 1 week and their elastic properties may well degrade with time. The initial high pressure of the Tensopress™ bandage did not appear to be beneficial and the pretibial skin necrosis observed in one patient following the application of Tensopress™ bandages is a potentially serious complication. Tensopress™ is more expensive than Elastocrepe™; Tensopress™ costs £4·38 and Elastocrepe™ £2·54 per bandage (Smith and Nephew, personal communication). If this difference is multiplied by 100 patients receiving one bandage every 2 weeks for 1 year, a saving of almost £5000 could be made in a single clinic.

This study has confirmed that initial ulcer size is the most important variable in determining whether an ulcer will heal. This has been observed by others[15] and suggests that ulcer trials should always be stratified according to initial ulcer size.

These results differ from those reported by Callam and colleagues[13]. The proportion of ulcers healed in both groups in the present study was comparable with the healing rate achieved with Tensopress™ in the Callam study (54 per cent over 12 weeks). The healing rate of 62 per cent with Elastocrepe™ in the present study, however, was higher than the 28 per cent reported by Callam *et al.* There are a number of possible reasons for this. First, different bandage systems were used in the two studies: the Tensopress™ group in the Callam study had orthopaedic wool, Tensopress™ and tubular retaining bandages (Tensoshape™). The Elastocrepe™ group had orthopaedic wool, Elastocrepe™ and a cotton-Lycra™ retaining bandage (Tensoplus™ Forte, Smith and Nephew). In the present study, paste bandages and tubular retaining bandages were applied to all patients. The elastic bandages may be more effective than inelastic systems, as suggested by Callam *et al.* This seems unlikely because the use of paste bandages next to the skin in both arms of the present study was likely to increase the element of inelastic compression in both groups. It is possible that the ulcers in the two groups in Callum's trial were not distributed equally as ulcers were not stratified by size; the mean ulcer size was 8·2 cm^2 in the Tensopress™ group compared with 11 cm^2 in the Elastocrepe™ group, although allowance was made for this by including the square root of the initial ulcer size as a covariate in the Cox model survival analysis. There could also have been differences in the patient populations in the two studies. A Mantel–Haenszel test for heterogeneity gave a statistically significant risk ratio ($P = 0·013$) and statistical analysis of the odds ratio gave a P value of 0·028.

The present study suggests that there is little benefit in adding higher compression as a means of speeding ulcer healing and very high pressure may be harmful. Most ulcers heal with adequate compression within 26 weeks, and few ulcers heal after this time. The late healing phase may be a worthwhile period to assess newer, potentially more effective treatments. It is possible that the paste bandaging has affected the rate of ulcer healing; the unit is currently conducting a 52-week study of three-layer paste and four-layer bandaging that will address both of these issues.

It is possible that the small sample size in this study has obscured a real difference; this trial had only 50 per cent power to detect a difference of 20 per cent at the 95 per cent significance level. A sample size of approximately 4000 ulcers would be required for an 80–90 per cent power to detect a 20 per cent difference. It would be difficult to recruit this number of patients for such a study.

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Randomized trial

Randomized trial of Lichtenstein *versus* Shouldice hernia repair in general surgical practice

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Background: The aim of the present randomized trial was to compare the Shouldice procedure and the Lichtenstein hernia repair with respect to recurrence rate, technical difficulty, convalescence and chronic pain. A further aim was to determine to what extent general surgeons in routine surgical practice were able to reproduce the excellent results reported from specialist hernia centres.

Methods: Three hundred patients with primary inguinal hernia were randomized to either a Shouldice repair or to a tension-free Lichtenstein repair. In a pretrial training programme the five participating general surgeons were taught to perform the two techniques in a standard manner. Follow-up was performed after 8 weeks, 1 year and 3 years. The last examination was performed by an independent blinded assessor.

Results: There was a significant difference in operating time in favour of the Lichtenstein technique. After a follow-up of 36–77 months seven recurrences were found in the Shouldice group (95 per cent confidence interval (c.i.) 1·3 to 8·1) and one in the mesh group (95 per cent c.i. 0·0 to 2·0). Chronic groin pain was reported by 4·2 and 5·6 per cent in the Shouldice and Lichtenstein groups respectively. It was characterized as mild or moderate in all except two patients who had the Shouldice operation.

Conclusion: Lichtenstein hernia repair was easier to learn, took less time and resulted in fewer recurrences. It was possible to achieve excellent results with this technique in a general surgical unit.

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Introduction

Reports on the outcome of inguinal hernia surgery show that the recurrence rate 5 years after operation can vary from 0·1 to over 20 per cent. Few other surgical operations have this kind of variation. One way to reduce the variation is to avoid the influence of experience on outcome[1–3]; surgeons should employ a standard method. The present trial, run in a general surgery centre, compared the Shouldice[4] and Lichtenstein[5,6] techniques.

Patients and methods

This randomized study was performed at the general surgical unit of Östersund Hospital. Three hundred men with a primary inguinal hernia, referred to one of the five participating surgeons between September 1994 and February 1998, were randomized to either Shouldice or Lichtenstein hernia repair. The Regional Ethics Committee approved the study.

Patients

Patients eligible for participation were men between 25 and 75 years of age with a clinically manifest, unilateral and primary inguinal hernia. Exclusion criteria were irreducibility, femoral hernia, coagulation abnormalities, anticoagulant treatment, and patients for whom anaesthesia was considered unsuitable. Obesity, huge hernias or scrotal hernias did not disqualify from participation. Verbal and written consent was obtained from each patient.

Randomization and data

The randomization process was computer generated in blocks (ten patients per group). Just before the skin incision was made one of the consecutively numbered sealed envelopes was opened. Data were recorded and transferred to a database.

Participating surgeons

In a pretrial training programme the five participating general surgeons were taught to perform Shouldice and Lichtenstein hernia repair in a standard manner. When all five were thoroughly familiar with both techniques, the trial was started.

Operative techniques

The Shouldice repair was performed as described by Devlin[7]. Four rows of 2/0 Prolene (Ethicon, Edinburgh, UK) were used for the herniorrhaphy. The tension-free mesh repair was performed as described by Lichtenstein *et al.*[5,6]. The mesh (Marlex; C. R. Bard, Billerica, Massachusetts, USA) was fixed with 2/0 Prolene. Prophylactic antibiotics were not used.

Anaesthesia

Surgery was performed under regional or general anaesthesia in accordance with the patient's preference or the anaesthetist's opinion. At the end of the operation 0·25 per cent bupivacaine was injected into the wound.

Postoperative care

No restrictions concerning activities were given. Sick leave was prescribed routinely for no more than 2 weeks initially and extended 1 week at a time when indicated.

Recorded variables

Preoperative variables such as age, type of work (heavy, light or desk work) and testicle size on the side for operation were recorded. Peroperative parameters were type of hernia, type of anaesthesia and peroperative complications. The duration of operation was registered; operations lasting 70 min or more were considered prolonged and indicative of technical difficulty. Postoperative pain was measured with a visual analogue scale (VAS). Complaints about urination and length of time spent in the hospital were registered.

Follow-up

Eight weeks after operation a specially trained nurse performed a follow-up examination. The patients were asked about persisting pain, i.e. pain after the operation (VAS), complete recovery time and number of days on sick leave. After 1 year all patients completed a questionnaire containing questions concerning recovery and pain. Patients with persisting discomfort or incomplete recovery were examined clinically. Recovery was defined as incomplete when discomfort in the operated groin interfered with normal daily activities.

Three years after surgery an examination was carried out by a surgeon who was not informed about the surgical technique used. This independent assessor was blindfolded and examined the patients with respect to the condition of the operated groin, the intensity and distribution of any persisting pain according to nerves, and the presence or absence of testicular atrophy. Recurrence was defined as a clinically manifest bulge or a protrusion exacerbated by a Vasalva manoeuvre in the operated groin[8]. In patients with inconclusive clinical findings, herniography was performed.

The clinic is aligned to 'the Swedish Hernia Register'[9] in which patients are followed until death or reoperation, so the outcome of all hernia repairs performed during the study period in this unit is available.

Statistical analysis and sample size calculation

Statistical analyses were performed with the SPSS program (SPSS, Chicago, Illinois, USA). Significance was tested with non-parametric tests as described by Siegel[10].

With an assumed difference in recurrence rate between the Lichtenstein and Shouldice methods of at least 0 and 5 per cent respectively, and a test power of 80 per cent, $\alpha = 0{\cdot}05$, each group required 152 patients[11].

Results

Three hundred men were randomized, of whom three were excluded. In one patient the surgeon did not find a hernia and two other patients changed their mind after randomization and opted out. The remaining 297 patients all attended the 8-week review while 296 filled in the 1-year questionnaire and 284 attended the final 3-year follow-up. During the study four patients died from causes unrelated to hernia surgery. In three patients the surgeon chose to convert the operation from the Shouldice repair to the Lichtenstein technique; all were technically difficult and extensive. These patients were kept in the groups to which they had originally been randomized so all data were analysed on an intention-to-treat basis.

Preoperative and peroperative variables

Age, type of work and type of hernia were equally distributed between the groups. Regional anaesthesia was given in 213, general in 69, and regional complemented with general anaesthesia in 15 operations. The type of anaesthesia was distributed equally between the groups (*Table 1*). There was only one significant postoperative complication, a minor perforation of the urinary bladder.

The mean duration of operation was 54 min for the Lichtenstein technique compared with 61 min for the Shouldice method ($P < 0·01$, Mann–Whitney U test) (*Table 1*). All five surgeons took less time for the Lichtenstein technique. In the Shouldice group 37 of the 148 operations lasted 70 min or more and were therefore considered prolonged. The corresponding number for the Lichtenstein group was 15 of the 149 operations ($P < 0·01$).

Postoperative variables

There were no major complications related to the operation and no reoperations. Nor were any significant differences found in the other postoperative variables (*Table 2*). The few infections that occurred were superficial, with the exception of one scrotal infection that later caused testicular atrophy. None of the infections led to a persistent sinus and none of the prostheses required removal.

Seventy-four patients complained of difficulty with urination that prolonged their hospital stay. Sixty-four of these patients had surgery under regional anaesthesia. Three patients had to be catheterized after the operation but none required an indwelling catheter. There was no association between the method of repair and complaints about voiding.

Testicular atrophy was seen in one patient after a deep scrotal infection as described above. Another patient developed atrophy after a painful postoperative orchitis. Both patients belonged to the mesh group.

The duration of hospital stay did not differ between the two groups. Sick leave was shorter with the Lichtenstein technique, but the difference was not significant (*Table 1*).

Table 1 Peroperative and postoperative data for hernia repair

	Shouldice (n = 148)	Lichtenstein (n = 149)
Anaesthesia		
General	32	37
Regional	106	107
General and regional	10	5
Operating time (min)*	61 (35–150)	54 (30–105)†
Hospital stay (h)*	13 (2–48)	15 (1–96)
Sick leave (days)*	18 (0–56)	15 (0–35)

*Values are mean (range). †$P < 0·01$ *versus* Shouldice (Mann–Whitney U test)

Table 2 Postoperative complications after hernia repair

	Shouldice (n = 148)	Lichstenstein (n = 149)
Haematoma	2 (1·4)	4 (2·7)
Infection	3 (2·0)	6 (4·0)
Seroma	0 (0)	1 (0·7)
Swelling	1 (0·7)	1 (0·7)
Urinary complaints	42 (28·4)	32 (21·5)
Testicular atrophy	0 (0)	2 (1·3)

Values in parentheses are percentages. There were no significant differences between groups

Pain and recovery

Most patients characterized the postoperative pain as slight. However, two patients had persistent moderate pain after Shouldice repair. This was classified as neuralgia on account of its radiation along an inguinal nerve. There were no other significant differences in pain between the two groups at any time during follow-up (*Table 3*). Persistent discomfort, if present, was considered mild by all patients.

Recurrence

At a follow-up of between 36 and 77 months, seven recurrent hernias were found in the Shouldice group (95 per cent confidence interval (c.i.) 1·3 to 8·1) compared with one in the Lichtenstein group (95 per cent c.i. 0·0 to 2·0). Three recurrences developed within 1 year of surgery and the remaining five were discovered at the 3-year follow-up. All eight patients with recurrence had their initial surgery under regional anaesthesia.

Table 3 Pain and recovery after hernia repair

	Shouldice	Lichtenstein
Pain (VAS 1–10)		
Postoperative	3·8 (n = 148)	3·6 (n = 149)
8 weeks	1·7 (n = 148)	1·7 (n = 149)
Persistent pain (%)		
8 weeks	3·4 (n = 148)	4·0 (n = 149)
1 year	6·1 (n = 148)	5·4 (n = 148)
3 years		
Mild	0·7 (n = 142)	4·9 (n = 142)
Moderate	2·1 (n = 142)	0·7 (n = 142)
Neuralgia	1·4 (n = 142)	0·0 (n = 142)
Full recovery (%)		
8 weeks	95·3 (n = 148)	94·0 (n = 149)
1 year	89·2 (n = 148)	91·2 (n = 148)
3 years	92·5 (n = 142)	93·0 (n = 142)

VAS, visual analogue scale. There were no significant differences between groups

Table 4 Type of primary hernia and recurrence

	Shouldice (n = 148)		Lichtenstein (n = 149)	
Primary hernia	Operations	Recurrence	Operations	Recurrence
Direct	47	4 (9)	41	0 (0)
Indirect	84	1 (1)	84	0 (0)
Combined	9	1 (11)	14	0 (0)
Sliding	8	1 (12)	10	1 (10)
All types	148	7 (4·7)	149	1 (0·7)

Values in parentheses are percentages

Recurrence in the Shouldice group occurred in four direct hernias, one indirect hernia, one combined hernia and one sliding hernia (*Table 4*). The only recurrence in the Lichtenstein group occurred after surgery for a sliding hernia. So far, only three of the eight recurrent hernias have required further surgery: a femoral hernia after Lichtenstein repair, and a femoral and a direct hernia after Shouldice repair.

There was no association between postoperative complications and recurrence. Nor was there any correlation between the individual surgeon and recurrence rate.

Discussion

Epidemiological data and data from the Swedish Hernia Register suggest that recurrence occurs after as many as 12–18 per cent of all conventionally repaired inguinal hernias[12,13]. These dismal figures contrast sharply with the recurrence rate of 0·1 per cent reported from the Lichtenstein Institute and the rate of less than 1 per cent observed at the Shouldice Hospital many years after surgery. Specialist units report results that are a factor of ten better than those of non-specialist centres. Since surgery contains an element of craftsmanship that distinguishes it from other branches of medicine[2], experience with a method leads to better results[3].

The aim of this trial was to compare the Shouldice and Lichtenstein hernia repairs in a non-specialist centre. A pretrial training programme ensured that all the participating surgeons were equally conversant with both methods.

It is known that observer error tends to deviate in the direction of the expectation[14]. The simple technique of blindfolding protected against this type of bias. In the present trial an independent assessor, unaware of the patient's type of operation, performed the final 3-year follow-up. Herniography was used in doubtful cases.

In the Shouldice group a recurrence rate of 4·7 per cent was observed with a follow-up of between 3 and 6 years. The technique as practised in the Shouldice Hospital has given better results with a recurrence rate of less than 1 per cent[4]. A few other specialist hernia surgeons have been able to reproduce these achievements[15,16]. However, in randomized controlled trials the recurrence rate is often higher and approaches 5 per cent[17,18]. The present results were in keeping with these reports. In the Lichtenstein group the recurrence rate was less than 1 per cent; the difference between specialist and non-specialist units appears to be less marked and the present results were in accordance with an earlier survey[19].

The significant difference in the duration of operation in favour of the Lichtenstein method is worthy of note. All five participants needed less time for the mesh procedure. Duration of operation is a surgeon-related variable[1] that reflects the ease of an operation. The smaller difference in recurrence rates between specialist and non-specialist units was further evidence of the simplicity of the operation. When a method is easy to learn, a high standard is quickly acquired and the results of general surgical units will tend to approach those obtained by specialists.

The Shouldice technique required considerable time to learn and in spite of the pretrial training programme difficulties were sometimes met when trying to accomplish repair at the inguinal floor without tension. Breakdown according to type of hernia suggested that direct hernias and hernias with a direct component were mainly responsible for the difference in recurrence rate between the two treatment groups.

The results of the present study were in keeping with those of earlier trials comparing the same techniques[20–22] and also with a report from the EU Hernia Trialists Collaboration[23], a systematic review of all randomized trials comparing open mesh with open non-mesh methods. The results were also in accordance with data from the Swedish Hernia Register, which has detailed information on approximately 37 000 hernia repairs mainly performed by non-specialist Swedish surgeons[24].

Deep infection[25] and chronic pain[26,27] have been concerns associated with the use of mesh. In this study there was no evidence of these complications.

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Randomized clinical trial of suture repair, polypropylene mesh or autodermal hernioplasty for incisional hernia

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Background: Since conventional suture repair for incisional hernia is associated with high recurrence rates, alloplastic and autoplastic prosthetic techniques have been suggested.

Methods: In a randomized trial, 160 patients with simple or complex hernias underwent either suture repair, autodermal skin graft or onlay polypropylene mesh repair. Suture repair was not done in complex hernias. This report concerns a planned interim analysis.

Results: At mean follow-up of 16 months, there were 17 hernia recurrences that were distributed similarly between the surgical techniques. There were fewer infectious complications after suture repair (three of 33 patients) than after skin graft or mesh repair (seven of 39 and five of 28 for simple hernias; seven of 31 and ten of 29 respectively for complex hernias) (*P* not significant). The severity of infections after polypropylene mesh implantation prompted the trial committee to discontinue the study. No differences were noted in duration of stay in hospital and quality of life. However, pain was significantly more frequent after polypropylene mesh repair (pooled risk ratio 2·9 and 1·8 at 6 weeks and 1 year respectively).

Conclusion: Suture repair was safe for small incisional hernias. Both autoplastic and alloplastic hernia repair yielded comparably low recurrence rates, but led to a high rate of wound infection.

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Introduction

Incisional hernia repair is one of the most common operations in general surgery. Incisional hernia can occur after all types of abdominal surgery; the risk lies between 11 and 15 per cent after midline laparotomy[1–4], and 0·2 and 1·2 per cent after laparoscopy[5]. Suture repair is the standard surgical treatment of incisional hernia; in Germany it is used in 85 per cent of primary and 63 per cent of recurrent incisional hernias[6]. Up to 55 per cent of these repairs, however, will fail[7–9].

In view of such data, methods of additional abdominal wall enforcement have been suggested. Principally, alloplastic and autologous materials are available, and the results for both seem comparable[10–13]. The use of non-absorbable mesh may lead to seroma, fistula and infection in the short term, and to foreign-body reaction, chronic local inflammation and mesh shrinkage in the long term[14–17]. Pain, paraesthesia, stiffness or even delayed infection are possible late complications. Mesh properties (material, pore size, filament structure), mesh position (onlay, inlay, sublay, intraperitoneal) and other factors (drainage, antibiotics) influence mesh safety[14, 15,18–20]. The use of autodermal skin graft as a biological material may evade such problems, but has never been tested in a randomized trial, because the technique has lost the wide popularity it once had[13].

This study was a three-armed randomized clinical trial comparing suture repair, mesh repair and autodermal hernioplasty for incisional hernia repair. The aim was to evaluate recurrence and complication rates as well as subjective outcomes and quality of life.

Patients and methods

Study population

The study was a double trial in which patients with an incisional hernia were randomized to one or three different techniques of hernia repair. Patients at a university hospital and a regional hospital were recruited between 1997 and

1999. Patients were considered eligible if they had an incisional hernia, defined as a palpable fascia or muscle defect at the site of a previous abdominal incision. Hernias were detected clinically and measured by ultrasonography. Patients with general contraindications for laparotomy or laparoscopy were excluded.

Two groups of patients were included. The 'simple' hernia group consisted of patients with a hernia less than 10 cm in diameter at preoperative ultrasonography who were undergoing surgery for the first or second time. These patients were allocated to one of the three study treatments. The 'complex' hernia group consisted of patients with a hernia that was either larger than 10 cm in diameter or was a re-recurrence. These patients were only allocated to mesh or autodermal hernioplasty, because previous experience suggested that suture repair was unsuitable for complex hernias[7]. All patients gave informed consent. The university ethics committee approved the study protocol.

Design and surgical procedures

Randomization was stratified for study centre. Allocation was concealed by the use of opaque, serially numbered envelopes. All surgeons had wide experience with all three techniques and two-thirds of procedures were done by a senior surgeon. All operations were performed under general anaesthesia.

The method of suture repair was Mayo fascia duplication with interrupted Ethibond no. 2 U-shaped sutures (Ethicon, Norderstedt, Germany). For mesh repair, polypropylene (Marlex; C. R. Bard, Billerica, Massachusetts, USA) was implanted as a suprafascial onlay, after direct suturing of the fascia with non-absorbable nylon sutures. The mesh was sized so that it overlapped by 6 cm in all directions. The mesh was fixed peripherally to the fascia with two interrupted 2/0 polyglactin (Vicryl; Ethicon) sutures and centrally with resorbable 2/0 polyglactin single-button sutures. The autodermal technique used a skin graft from the hernia region. After removal of epidermis and fat, the cutis mesh was implanted in an onlay technique[10]. The mesh had to overlap the suture line for 2 cm in all directions. It was fixed under tension with two continuous sutures (Ethibond no. 2). In all patients, fascia closure was possible before mesh implantation.

All patients received intravenous antibiotics at anaesthesia induction (a single dose of third-generation cephalosporin) and suction drainage. Postoperative care consisted of a hernia truss, opioid analgesia for the first day and oral analgesia thereafter. Drains were removed 48 h after operation at the latest. Low-dose heparin was continued until the fifth day after operation. Patients were informed about the type of surgery they had received and instructed to avoid heavy lifting during convalescence.

Outcome measures and data collection

The primary outcome measure was hernia recurrence. Follow-up examinations took place 3, 6, 12 and 24 months after the operation, or when any patient had a complaint. These examinations were planned to be single blind, but this was not possible because most patients mentioned the type of surgery they had received during their visit.

Complications served as a secondary outcome measure. Wound healing disorders were defined as any event that required reopening of the wound. Complications treatable by puncture and aspiration were not counted.

Other outcome measures included return to usual activities of daily life, pain and stiffness of the abdominal wall. Quality of life was measured by the Gastrointestinal Quality of Life Index (GIQL)[21]. GIQL scores were transformed into percentages with 100 per cent indicating maximum quality of life. One GIQL item was used to assess the cosmetic result of the operation separately. Pain was measured at only one of the two hospitals. A visual analogue scale was applied by the same person and at the same time of the day in all patients. The consumption of analgesic drugs as well as postoperative complications were documented daily until day 10.

Statistical analysis

Taking the three-armed design and follow-up losses into account, the aim was to recruit 200 patients with a simple hernia, which would give a chance of 80 per cent (with $\alpha = 5$ per cent) to detect an absolute difference of 20 per cent in rates of recurrence (e.g. 40 *versus* 20 per cent). An interim analysis was planned after recruitment of 100 patients. It was expected that the interim analysis would yield significantly more recurrences after suture repair; the plan was then to continue the trial as a two-armed study.

Primarily, data were analysed by intention to treat. Recurrence rates were analysed by Kaplan–Meier survival analysis and the log rank test. Parametric or non-parametric tests were used according to the distribution of continuous data. For pooling the risk ratios (RRs) of the two strata, meta-analytic software (RevMan 4.1; Cochrane Collaboration, Oxford, UK) was used.

Results

Patient characteristics and surgical management

Of approximately 200 eligible patients (retrospective estimation), 160 agreed to take part in the study; 100 had a simple and 60 had a complex incisional hernia. Eighty-four were recruited in the regional hospital. The clinical characteristics in the groups were similar at trial entry (*Table 1*).

In 12 patients (8 per cent), the procedure assigned by randomization was converted (*Fig. 1*). In half of these cases, the decision to convert was made before the operation had begun (non-compliance of the surgeon), while in other patients intraoperative difficulties led to a change in surgical technique. In the mesh group, one small bowel injury occurred, which was managed without clinical consequences. The duration of operation was shorter in the suture repair group (*P* not significant) (*Table 2*).

Clinical outcomes within hospital and after 6 weeks

During the first 10 days after operation, complications developed in 15 patients (15 per cent) with a simple hernia and 17 (28 per cent) with a complex hernia (RR 1·89 (95 per cent confidence interval (c.i.) 1·02 to 3·50)) (*Table 3*). Two patients with a large incisional hernia, whose operation was converted from autodermal to mesh repair, and two other patients who underwent mesh repair for a small hernia developed infections of such severity that mesh removal was required. In the latter two patients treatment lasted for over a year; in one a chronic infection of the abdominal wall led to fungaemic sepsis that required intensive care.

For simple hernias, the rate of infectious complications was lower after suture repair than after both other repairs (RR 0·51 (95 per cent c.i. 0·15 to 1·68)). When patients were analysed according to treatment received, polypropylene mesh implantation led to an increase in infectious complications in both simple and complex hernia repair. Although the pooled difference in complications reached only marginal statistical significance (RR 1·75 (95 per cent c.i. 0·93 to 3·29)), the clinical severity of these complications (together with the availability of new improved mesh materials) was considered a sufficient argument for stopping the trial. Despite the complications in some patients, postoperative hospital stay (*Table 2*) did not differ between

Table 1 Characteristics of patients at trial entry

	Simple hernia ($n = 100$)			Complex hernia ($n = 60$)	
	Suture repair ($n = 33$)	Polypropylene mesh ($n = 39$)	Autodermal graft ($n = 28$)	Polypropylene mesh ($n = 31$)	Autodermal graft ($n = 29$)
Mean(s.d.) age (years)	61(11)	60(13)	55(17)	59(10)	52(14)
Gender					
Male	15	19	10	18	14
Female	18	20	18	13	15
Specific risk factors					
Obesity*	8	11	12	10	11
Pulmonary disease	9	9	2	7	7
Smoking	6	6	5	11	14
Cardiac disease	14	16	8	9	7
Diabetes	2	5	3	3	3
Vascular disease	1	0	1	6	1
Renal disease	3	1	1	2	0
Constipation	1	6	3	1	3
Steroid treatment	1	1	0	2	2
Other	6	8	4	9	6
Mean(s.d.) hernia size (cm)					
Vertical diameter	5·8(3·0)	6·6(2·6)	6·1(2·5)	13·8(8·4)	11·3(5·6)
Horizontal diameter	3·6(1·7)	4·8(1·9)	4·4(1·8)	11·7(9·4)	8·8(6·0)
Site of hernia					
Midline (upper and/or lower)	24	26	19	23	22
Paramedian	5	4	1	2	0
Other or multiple	4	9	8	6	7
No. of previous hernia repairs					
None	26	28	16	11	13
One	7	11	12	5	3
Two	–	–	–	8	6
Three	–	–	–	5	6
Four or more	–	–	–	2	1

Data on obesity and hernia size missing for one and four patients respectively. *Body mass index 30 kg/m^2 or more

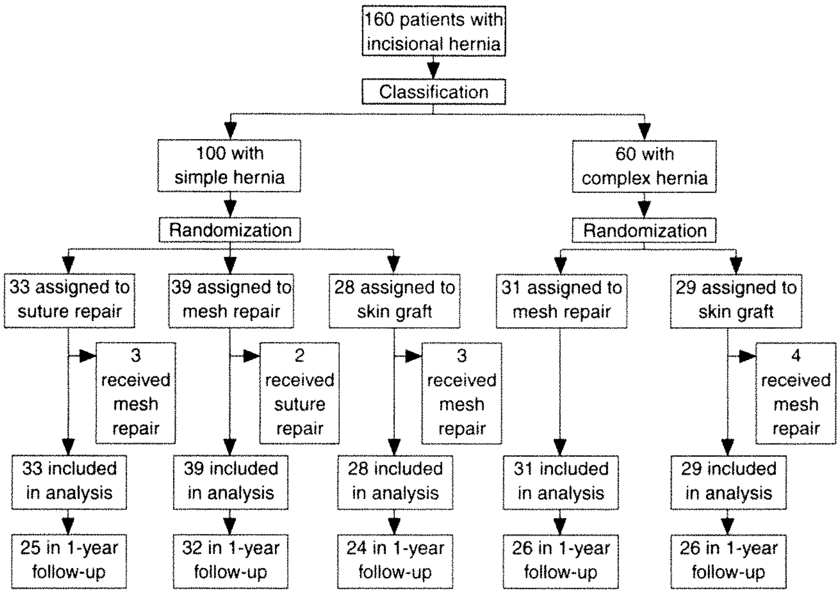


Fig. 1 Trial profile

Table 2 Short and long-term outcomes

	Simple hernia (n = 100)				Complex hernia (n = 60)		
	Suture repair (n = 33)	Polypropylene mesh (n = 39)	Autodermal graft (n = 28)	P	Polypropylene mesh (n = 31)	Autodermal graft (n = 29)	P
Short-term results							
Length of operation (min)*	54(31) (n = 33)	73(31) (n = 39)	67(19) (n = 28)	0·02§	90(35) (n = 31)	95(44) (n = 29)	0·64¶
Hospital stay (days)†	6 (5–7) (n = 33)	7 (6–12) (n = 39)	7 (5–10) (n = 28)	0·06**	8 (6–12) (n = 31)	7 (6–12) (n = 29)	0·78††
Results at 6 weeks							
Return to full activity (weeks)†	4 (4–12) (n = 19)	8 (4–12) (n = 25)	4 (3–8) (n = 14)	0·17**	8 (4–12) (n = 25)	8 (4–12) (n = 20)	0·49††
Pain intensity (VAS)†	0 (0–0) (n = 30)	0 (0–3) (n = 38)	0 (0–0) (n = 28)	0·01**	1 (0–3) (n = 30)	0 (0–0) (n = 27)	0·01††
Presence of pain (VAS > 0)	4 of 30	16 of 38	4 of 28	0·01‡‡	15 of 30	5 of 27	0·03‡‡
Results at 1 year							
Pain intensity (VAS)†	0 (0–1) (n = 24)	0 (0–3) (n = 30)	0 (0–0) (n = 23)	0·11**	0 (0–3) (n = 24)	0 (0–1) (n = 26)	0·53††
Presence of pain (VAS > 0)	6 of 24	12 of 30	4 of 23	0·17‡‡	11 of 24	7 of 26	0·24‡‡
Abdominal sensations (VAS)†	0 (0–2) (n = 24)	0 (0–2) (n = 30)	2 (0–2) (n = 23)	0·38**	1 (0–2) (n = 24)	1 (0–2) (n = 26)	1·00††
Quality of life (%)*‡	72(16) (n = 17)	75(15) (n = 26)	77(13) (n = 15)	0·63§	73(14) (n = 26)	72(14) (n = 17)	0·85¶
Unhappy with cosmetic result	7 of 17	8 of 24	6 of 14	0·81‡‡	10 of 25	8 of 16	0·75‡‡
Length of follow-up (months)†	13 (9–15)	14 (11–23)	14 (11–16)	0·21**	16 (12–24)	13 (12–15)	0·27††

*Values are mean(s.d.) or †median (25th and 75th percentiles). ‡A value of 100 per cent indicates perfect quality of life. VAS, visual analogue scale. §Analysis of variance; ¶t test; **Kruskal–Wallis test; ††Mann–Whitney U test; ‡‡χ^2 test

the three techniques. Return to normal activity was also similar among the groups.

Pain intensity at the 6-week follow-up was significantly different between the groups (P = 0·01 for simple hernia and P = 0·01 for complex hernia; Kruskal–Wallis test and Mann–Whitney U test respectively). Significant pain was 2·9 times (95 per cent c.i. 1·6 to 5·1) (P < 0·01) more likely after polypropylene mesh repair than suture or autodermal repair.

Late clinical outcome

A follow-up of at least 9 months was completed in 133 patients (83 per cent). Two patients died from causes unrelated to the operation and 18 (11 per cent) were lost to follow-up. A total of 17 recurrent hernias were detected, seven of which were early.

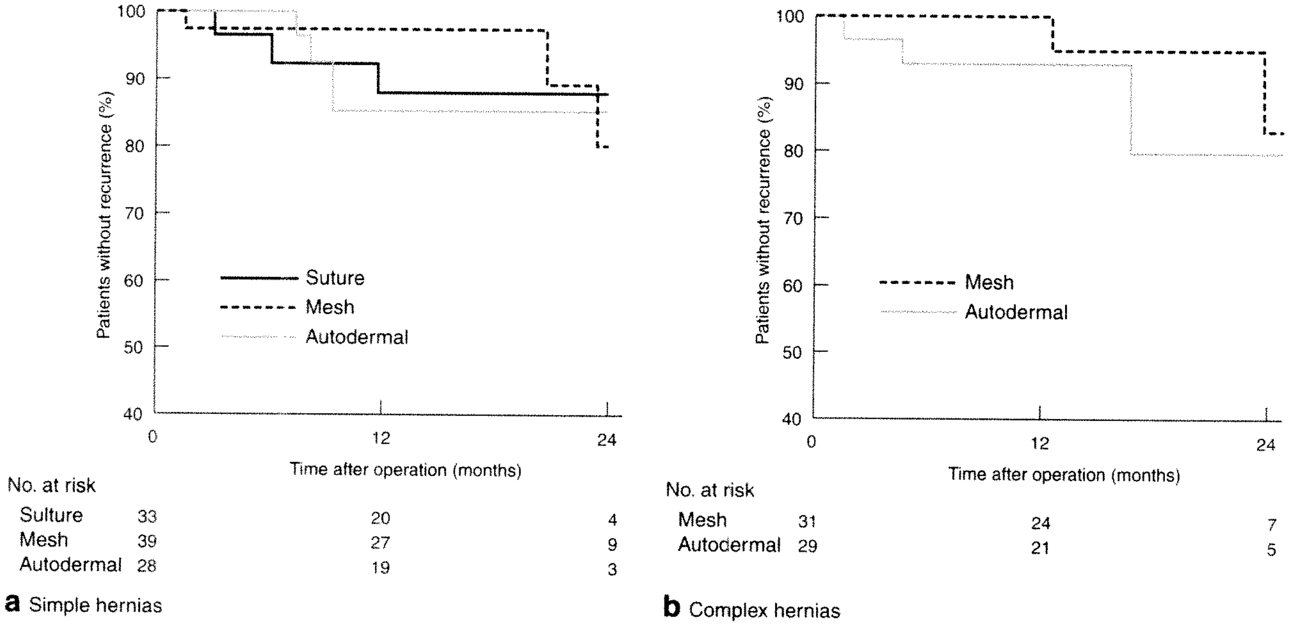
There were 11 recurrences in the 100 patients with repair of a simple hernia and six in the 60 patients with a complex hernia. Hernia recurrences were distributed evenly among the groups (*Fig. 2*), and statistical analysis gave no evidence for the superiority of any technique.

In the 127 patients who reported on pain, the rate of continued discomfort was higher after mesh implantation than after other techniques: the RR was 1·9 and 1·7 for simple and complex hernias respectively, equivalent to a

Table 3 Complications and hernia recurrences

	Simple hernia (*n* = 100)			Complex hernia (*n* = 60)	
	Suture repair (*n* = 33)	Polypropylene mesh (*n* = 39)	Autodermal graft (*n* = 28)	Polypropylene mesh (*n* = 31)	Autodermal graft (*n* = 29)
Local complications					
Infection	0	4	2	2	5
Haematoma	2	0	0	1	1
Seroma	1	3	1	4	3
Other	0	0	2*	0	1†
Total (intention to treat analysis)	3 of 33	7 of 39	5 of 28	7 of 31	10 of 29
Total (analysis as treated)	2 of 32	8 of 43	5 of 25	11 of 35	6 of 25
General complications					
Thromboembolic	1	0	0	0	1
Pneumonia	1	0	0	0	0
Stroke	0	0	0	1	0
Recurrence	4	3	4	3	3

Patients who developed more than one specific complication are listed only with the more severe complication. *Suture-thread sinus; †superficial skin necrosis



a Simple hernias

b Complex hernias

Fig. 2 Kaplan–Meier curves for recurrence after different methods of surgical repair of **a** simple (n = 100) and **b** complex (n = 60) hernias. There were no significant differences between recurrence rates (**a** P = 0·68 and **b** P = 0·48)

pooled estimate of 1·8 (95 per cent c.i. 1·1 to 3·1) ($P = 0{\cdot}03$). Patients who described continued pain reported its intensity to be similar among the different operations with a median of 3. Quality of life, as measured with the GIQL, was also similar among the treatment groups.

Discussion

Most treatment recommendations for incisional hernia repair originate from retrospective studies or case series, in which risk factors for hernia recurrence have been inadequately described and unevenly distributed. This randomized trial compared different basic techniques for simple and complex hernia repair and found similar recurrence rates. Bearing in mind previous publications, the overall recurrence rate of 11 per cent was unexpectedly low, and the trial failed to gain sufficient statistical power to establish a meaningful comparison of recurrence rates. A surprisingly high number of wound complications occurred after alloplastic and autoplastic prosthetic repairs. Considering the severity of these complications and their absolute rate in the analysis as treated, it was thought unethical to continue the trial. Furthermore, at the same time another trial suggested that the mesh material used in the study should be replaced by newer, possibly better materials[22].

It is not clear whether the significant wound infections after mesh herniorrhaphy arose from the onlay position of the mesh or its textile properties. Leber *et al.*[14] found differing infection rates among various mesh materials, but not between onlay and sublay repairs. It is known that bacteria are difficult targets for the immune system once they have reached alloplastic materials. This holds true especially for microporous meshes, but to a lesser extent also for meshes with large pores that allow immune cells to enter[16].

Another randomized clinical trial, by Schumpelick *et al.*[22], recently revealed that low-weight mesh materials can possibly prevent specific complications at the implantation site. They also noted a tendency towards less pain and mesh awareness in patients who received the new mesh material. Pain was a significant problem in the present study; it was not only more frequent after mesh repair but was also often still present 1 year after operation. This lends support to the theory that chronic inflammation develops in the vicinity of alloplastic materials, which causes the high frequency of pain after mesh repair[23,24].

In comparison to repair using alloplastic materials, the autodermal hernioplasty offers the advantages of avoiding a foreign-body reaction and high costs. However, while the present data showed acceptable recurrence rates (12 per cent) and no persistence of pain after autodermal hernioplasty, the incidence of local complications reached 26 per cent, above an acceptable limit. There is no randomized evidence that the sublay position for mesh insertion could lead to better results.

The present study was partly limited in its validity by problems such as an incomplete follow-up, patients in whom the procedure was changed, small sample size and a potential for selection bias. The last issue, however, was not critical, as about two-thirds of eligible patients were recruited into the trial. As the evaluation was unblinded, outcome criteria such as pain and hospital stay must be interpreted carefully. The fact that the GIQL did not show any differences among the groups while pain scores were different was explained by the low responsiveness of the GIQL in this group of patients. Many items in the GIQL address bowel function, which is usually unaffected by hernia or hernia repair; a more specific instrument to assess quality of life was not available. A small randomized trial from Italy suggested that pulmonary function was more impaired after primary suture than mesh repair[25]. Future trials should therefore assess breathing difficulties.

Based on a randomized trial of 181 patients, Luijendijk *et al.*[26] recently recommended mesh repair even for small hernias (less than 6 cm in diameter). Both the recurrence (40 and 20 per cent) and the infection rates (2 and 4 per cent for suture and mesh repair respectively) were in contrast to findings in the present study. However, the surgical technique for mesh repair and suture repair differed between the two studies. First, Luijendijk *et al.* fixed the mesh to the back of the abdominal wall and covered it with peritoneum or omentum (i.e. sublay position), while an onlay repair was used here. Second, fascia duplication was preferred in the current study, whereas the Dutch trial used fascia adaptation.

In conclusion, onlay polypropylene mesh repair and autodermal hernioplasty of incisional hernia carried a high risk of infectious complications in the current study. Therefore, conventional suture techniques may still have a place in the repair of a small incisional hernia.

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Original article

Liver fibrosis increases the risk of intrahepatic recurrence after hepatectomy for hepatocellular carcinoma

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Background: Hepatocellular carcinoma (HCC) commonly develops in patients with chronic hepatitis. Intrahepatic recurrence after hepatectomy often includes nodules of new tumour in the liver remnant. The aim of this study was to examine hepatitis-related factors that might predict this type of recurrence.
Methods: The influence of various hepatitis-related factors on intrahepatic recurrence of HCC was studied by multivariate analysis in 138 patients who underwent curative resection and were followed for more than 2 years.
Results: The Cox proportional hazard model showed that histological evidence of fibrosis of the underlying liver was the most significant predictive factor for intrahepatic recurrence ($P = 0{\cdot}001$). Serum albumin level was also significantly associated with recurrence ($P = 0{\cdot}038$). The relative risks of histological fibrosis and low serum albumin levels were 8·9 and 1·7 respectively. Among tumour-related factors, only tumour size was significantly associated with recurrence ($P = 0{\cdot}017$). Major hepatectomy was also an independent risk factor for intrahepatic recurrence ($P = 0{\cdot}004$).
Conclusion: Histological evidence of fibrosis and low serum albumin levels are useful predictors of intrahepatic recurrence after hepatectomy, presumably owing to metachronous multifocal tumour in the liver remnant.

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Introduction

The long-term results of surgery for hepatocellular carcinoma (HCC) are not satisfactory, primarily because of the high incidence of intrahepatic tumour recurrence[1,2]. HCC commonly develops in patients with chronic hepatitis following hepatitis B or hepatitis C infection[3,4]. This unique feature might be the cause of intrahepatic recurrence of HCC due to metachronous multicentric hepatocarcinogenesis in the liver remnant even after complete resection of the primary tumour[5,6]. While the prognostic significance of various pathological and molecular biological factors with respect to tumour characteristics has been reported[7,8], little attention has been paid to the influence of 'field change' of the underlying liver disease.

It is important to know the potential risk of multicentric hepatocarcinogenesis when selecting patients for surgical resection, liver transplantation or less invasive local ablation[9–13]. A previous study suggested that chronic aggressive hepatitis is a risk factor for intrahepatic recurrence of HCC after hepatectomy, rather than chronic persistent hepatitis[14]. Desmet *et al.*[15] postulated a new histological classification of chronic hepatitis, including a separate scoring system for the necroinflammatory activity and fibrosis. This scoring system could be useful in predicting the potential of new hepatocarcinogenesis in the liver remnant after resection of a primary HCC. The aim of this study was to evaluate the influence of these histological variables of underlying chronic hepatitis and other hepatitis-related factors on intrahepatic recurrence after surgical resection of HCC.

Patients and methods

From 1983 to 1996, 173 patients with HCC were treated by hepatectomy at Nara Medical University Hospital, Kashihara, Japan. Twenty of these patients who did not undergo curative resection were excluded from the study. Curative resection was defined as complete resection of all macroscopically detectable tumour with histological tumour clearance (the entire tumour mass was included in the surgical specimen without exposure of tumour cells on the cut edge). Fifteen patients who died from postoperative complications or other diseases within 24 months were also excluded. The remaining 138 patients, who have been followed for at least 24 months as outpatients, were the subject of this study. There were 111 men and 27 women of mean age 60 (range 29–79) years. Some 34 (25 per cent) were seropositive for hepatitis B virus surface antigen (HBs-Ag) and 79 (70 per cent) of 113 patients tested were seropositive for hepatitis C virus antibody (HCV-Ab). HCV-Ab testing was available from 1988. Twelve patients were negative to both HBs-Ag and HCV-Ab.

Operations

The operative procedure was selected on the basis of the extent of the tumour and the hepatic functional reserve, which was assessed by Child's classification, indocyanine green retention test, hepaplastin test and oral glucose tolerance test. The extent of hepatectomy was defined according to the functional anatomy of the liver[16]. Right or left hepatectomy and segmentectomy were classified as major hepatectomy; subsegmentectomy and partial hepatectomy were classified as minor hepatectomy.

Histological variables of underlying chronic hepatitis

The histological status of the underlying chronic hepatitis was classified using the microscopic findings of the non-cancerous part of the surgical specimen by haematoxylin and eosin staining. The criteria established by Desmet *et al.*[15] were used including 'grading' and 'staging', which represented the necroinflammatory activity and fibrosis respectively. Grading was scored as 1 (minimal), 2 (mild), 3 (moderate) and 4 (severe). Staging was scored as 0 (no fibrosis), 1 (mild), 2 (moderate), 3 (severe) and 4 (liver cirrhosis).

Hepatitis-related variables in blood

The seropositivity of HBs-Ag and HCV-Ab was tested, and the serum total bilirubin, alanine aminotransferase (ALT) and albumin levels were measured in all patients before hepatectomy.

Follow-up

Liver function tests were carried out and levels of α-foetoprotein and protein induced by vitamin K absence were measured every 3 months. Chest radiography, ultrasonography, computed tomography and/or magnetic resonance imaging were performed every 4 months. When recurrence was indicated by any of these examinations, patients underwent hepatic angiography. Some recurrent nodules were confirmed by percutaneous biopsy or repeat hepatectomy (12 patients). No patient received postoperative adjunctive therapy before detection of the recurrence.

Location of intrahepatic recurrence

The site of the intrahepatic recurrence was correlated with the location of the primary tumour. The sites of recurrent tumour at the time of initial recurrence were classified as: (1) same lobe intrahepatic recurrence – only in the lobe ipsilateral to the primary tumour; (2) opposite lobe recurrence – only in the contralateral lobe; and (3) both lobes – two or more recurrent nodules found in both lobes, independent of the site of the primary tumour. Patients with bilobar primary HCC were excluded from this analysis.

Statistical analysis

Cumulative recurrence-free survival rates after hepatectomy were obtained by the Kaplan–Meier method, and compared by the log rank test among groups for univariate analysis. The predictive factors influencing the intrahepatic recurrence of HCC were analysed by means of the Cox multivariate proportional hazard model using StatView 5.0 software (SAS Institute, Cary, North Carolina, USA). Variables including tumour factors, hepatitis-related factors and operative factors were entered into the multivariate analysis. $P < 0{\cdot}05$ was considered statistically significant.

Results

Eighty-eight of the 138 patients developed intrahepatic recurrence during follow-up. Factors listed in *Table 1* were analysed for recurrence-free survival. Univariate analysis showed statistical significance for tumour size ($P = 0{\cdot}008$), vascular involvement ($P = 0{\cdot}049$), ALT ($P = 0{\cdot}010$), albumin ($P = 0{\cdot}003$), grading ($P = 0{\cdot}020$), staging ($P = 0{\cdot}010$) and extent of hepatectomy ($P = 0{\cdot}022$). Multivariate analysis by the Cox proportional hazard model showed that the most predictive variable for recurrence in this model was staging of the underlying chronic hepatitis, which represented the degree of liver fibrosis (*Table 2*). Serum albumin levels and extent of hepatectomy also showed independent predictive significance. Another histological variable, grading, which represented necroinflammatory activity of the underlying hepatitis, did not show statistical significance in the multivariate analysis. Of the tumour-related factors, only tumour size was significant for recurrence-free survival after hepatectomy for HCC in the multivariate analysis. Major hepatectomy was also an independent predictive factor of intrahepatic recurrence (*Table 2*).

Table 1 Cox multivariate proportional hazard model for predictive variables for intrahepatic recurrence (n = 138)

Variable	Categorization	χ^2	P
Age (years)	0–50, 51–60, 61–70, ≥ 71	6·63	0·085
Sex	Female, male	0·15	0·701
Tumour-related factors			
Tumour size (cm)	≤ 5·0, > 5·0	5·66	0·017
No. of tumours	Solitary, multiple (≥ 2)	1·20	0·273
Vascular involvement	Absent, present	1·47	0·226
UICC pTNM stage	I, II, III, IVA	5·75	0·125
α-foetoprotein (ng/ml)	0–20, 21–100, ≥ 101	1·34	0·513
Edmondson–Steiner grade	I, II, III, IV	0·90	0·925
Hepatitis-related factors			
HBs-Ag	Negative, positive	0·35	0·556
Anti-HCV-Ab	Negative, positive, not tested*	3·34	0·188
Total bilirubin (mg/dl)	≤ 1·0, > 1·0	0·58	0·446
ALT (units/l)	0–50, 51–100, ≥ 101	2·51	0·285
Albumin (g/dl)	< 3·5, ≥ 3·5	4·29	0·038
Grading†	1–2, 3–4	0·07	0·795
Staging‡	0–1, 2–4	10·52	0·001
Operation-related factors			
Extent of hepatectomy	Major§, minor¶	8·51	0·004
Surgical free margin (cm)	< 1·0, ≥ 1·0	0·04	0·834

*Not tested in 25 of 138 patients. †Histological necrosis and inflammation score of the underlying chronic hepatitis; ‡histological fibrosis score of the underlying chronic hepatitis. §Right or left hepatectomy or segmentectomy; ¶subsegmentectomy or partial hepatectomy. UICC pTNM, Union Internacional Contra la Cancrum pathological tumour node metastasis classification; HBs-Ag, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; ALT alanine aminotransferase

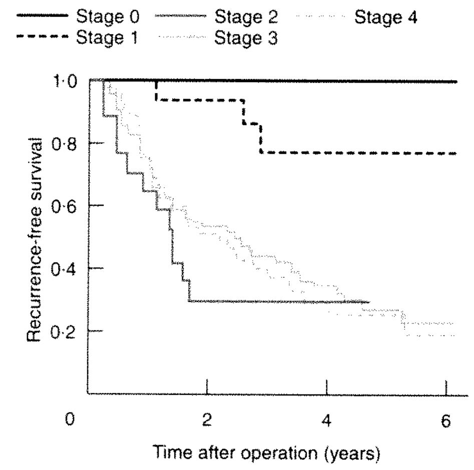
Table 2 Relative risk of significant predictive factors in Cox analysis of intrahepatic recurrence

Variable	Relative risk
Staging 2–4	8·9 (2·3, 30·0)
Major hepatectomy	2·6 (1·4, 4·8)
Tumour size > 5·0 cm	2·3 (1·2, 4·6)
Albumin < 3·5 g/dl	1·7 (1·1, 2·9)

Values in parentheses are 95 per cent confidence intervals

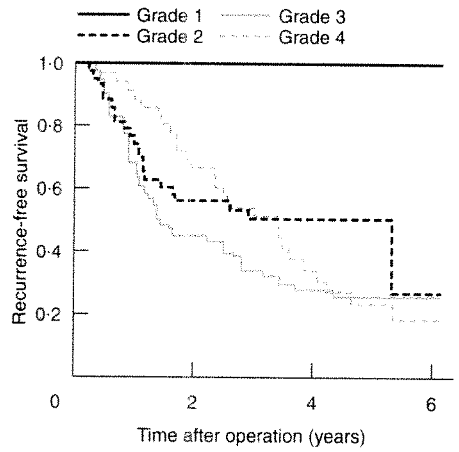
The cumulative recurrence-free survival rates according to the two histological variables of the underlying chronic hepatitis are shown in *Figs 1* and *2*. A marked difference was seen between stages 0–1 and 2–4 (*Fig. 1*). While grading did not show predictive significance in the multivariate analysis, only grade 1 patients had a good prognosis in the univariate analysis (*Fig. 2*). Patients with low serum albumin levels had a significantly lower recurrence-free survival rate.

A model was constructed to predict intrahepatic recurrence using a combination of tumour size and staging, the most significant tumour-related and hepatitis-related factors in the multivariate analysis. The cumulative 5-year recurrence-free survival rates in patients with stage 0–1 and stage 2–4 fibrosis with a small (5 cm or less) tumour, and



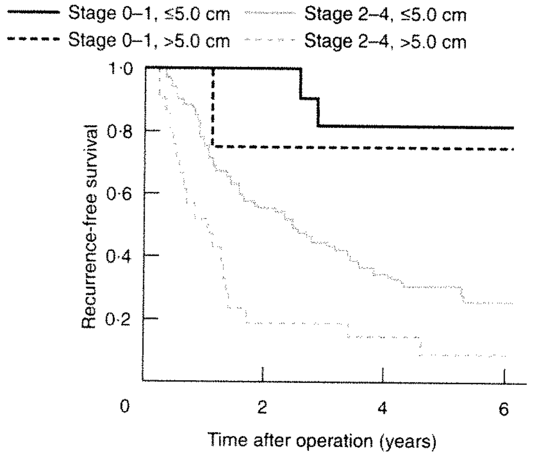
No. at risk				
Stage 0	2	2	2	2
Stage 1	16	15	7	2
Stage 2	17	5	3	0
Stage 3	45	23	9	2
Stage 4	58	30	17	6

Fig. 1 Recurrence-free survival according to the fibrosis of the underlying liver (staging). Patients with stage 0 (no fibrosis) and 1 (mild) had a significantly lower recurrence rate than those with stage 2 (moderate), 3 (severe) and 4 (cirrhosis) (P = 0·001, log rank test)



No. at risk				
Grade 1	6	6	6	3
Grade 2	42	23	12	1
Grade 3	55	24	10	6
Grade 4	35	22	10	2

Fig. 2 Recurrence-free survival according to the necroinflammatory activity of the underlying hepatitis (grading). While patients with grade 1 (minimal) inflammation had a good prognosis ($P = 0{\cdot}020$ *versus* grades 2–4, log rank test), no significant difference was seen between patients with grade 2 (mild), 3 (moderate) or 4 (severe) inflammation



No. at risk				
Stage 0–1, ≤5.0 cm	14	14	8	3
Stage 0–1, >5.0 cm	4	3	1	0
Stage 2–4, ≤5.0 cm	99	54	26	8
Stage 2–4, >5.0 cm	21	4	3	1

Fig. 3 Recurrence-free survival using a combination of stage of the underlying hepatitis and tumour size (up to 5 cm or more than 5 cm). Patients with minimal liver fibrosis (stage 0–1) had a significantly higher recurrence-free survival rate than patients with a high stage (stage 2–4) and tumour size 5 cm or less ($P < 0{\cdot}001$, log rank test). A significant difference was also seen between tumour size up to 5 cm and more than 5 cm in patients with stage 2–4 fibrosis ($P = 0{\cdot}001$)

stage 2–4 fibrosis with a large (more than 5 cm) tumour were 81, 31 and 10 per cent respectively (*Fig. 3*).

The location of intrahepatic recurrent nodules according to staging is listed in *Table 3*. Eleven patients with bilobar primary HCC were excluded from this analysis. While intrahepatic recurrence was seen only in the ipsilateral lobe in patients with stage 0–1 fibrosis, intrahepatic recurrence frequently developed in the contralateral lobe in patients with stage 2–4 fibrosis (*Table 3*).

Table 3 Sites of intrahepatic recurrence in 82 patients with unilobar primary hepatocellular carcinoma

Degree of histological fibrosis	Sites of intrahepatic recurrence*		
	Ipsilateral lobe	Contralateral lobe	Both lobes
Staging 0–1	3	0	0
Staging 2–4	29	21	29

*Classified relative to the site of the primary tumour

Discussion

The present study showed that histological fibrosis of the underlying liver was the most significant risk factor for intrahepatic recurrence after curative resection of HCC. Among various tumour-related factors only tumour size had prognostic significance. The strong correlation between hepatitis-related factors and intrahepatic recurrence suggests that multicentric metachronous hepatocarcinogenesis, possibly promoted by the underlying chronic hepatitis, could play a major role. Twenty-one patients had intrahepatic recurrence in the lobe contralateral to the primary tumour without recurrence in the ipsilateral lobe, suggesting multifocal disease (*Table 3*).

The importance of fibrosis in hepatocarcinogenesis has been described in patients with chronic viral hepatitis[17–19]. The annual incidence of developing HCC increased with the progression of liver fibrosis during long-term follow-up of patients with hepatitis B and C[18,19]. Fibrosis of the liver is established through repetitive necroinflammation and regeneration in the liver with chronic hepatitis, and eventually progresses to liver cirrhosis[20]. Since this process requires vigorous mitosis of the hepatocytes in response to cell destruction, increased fibrosis is associated with a large amount of mitotic activity, which may allow accumulation of genetic transformations[21,22]. Sakaida *et al.*[23] reported that fibrosis induced hepatocarcinogenesis in a rat HCC model.

Of blood biochemistry, only serum albumin level showed predictive significance in the multivariate analysis. Serum albumin levels decrease in relation to the progression of chronic liver disease, so the values might represent the degree of liver fibrosis (the most significant predictive factor). Serum ALT levels, which may represent activity of hepatitis, did not show predictive significance for intrahepatic recurrence, in contrast to previous results[24]. The result of the present multivariate analysis suggested that accumulation of fibrosis during the progression of chronic hepatitis (staging) was more important for potential hepatocarcinogenesis than intensity of the necroinflammatory activity of hepatitis (grading).

Although extended resection usually improves the long-term result of operation, in the present study the need for major hepatectomy increased the risk of intrahepatic recurrence. It is not known whether extended hepatectomy promoted hepatocarcinogenesis in the remnant liver by increasing the need for regeneration; this possible mechanism remains speculative[25].

The significant potential of multicentric hepatocarcinogenesis in patients with HCC may justify liver transplantation at an earlier stage[2,10,14]. The present study indicated that the potential of multicentric hepatocarcinogenesis is low in patients with mild liver fibrosis, who could be treated by surgical resection. In patients with significant liver fibrosis, liver transplantation could be considered. However, it must be noted that the recurrence rate is very high even after liver transplantation in patients with advanced tumours, mainly owing to occult extrahepatic metastasis before transplantation[10,26].

Histological evaluation of the underlying chronic hepatitis by percutaneous biopsy of the non-cancerous part of the liver may be a useful way of selecting the appropriate treatment for HCC. The combination of histological fibrosis of the liver and tumour size might provide a useful model for predicting intrahepatic recurrence.

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Original article

Preoperative hepatic venous embolization for partial hepatectomy combined with segmental resection of major hepatic vein

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Background: Liver resection of segments VII and/or VIII sometimes requires segmental resection of the right hepatic vein in patients with liver tumours invading or located close to the hepatic vein. In this situation, hepatic vein reconstruction is thought to have an important role in the postoperative function of segment VI. This study investigated whether preoperative embolization of the major hepatic vein could obviate the need for hepatic vein reconstruction after cranial partial resection of the liver including the major hepatic vein trunk in a preclinical model.

Methods: Sixteen beagles were divided into two groups of eight: control group (hepatectomy alone) and hepatic venous embolization (HVE) group (hepatectomy after HVE). HVE was performed 2 weeks before hepatectomy. All dogs underwent resection of the cranial third of the left lateral liver lobe together with the major trunk of the left hepatic vein. Following hepatectomy, survival, histological features, portal venous pressure and serum aspartate aminotransferase (AST) levels were determined.

Results: Six control animals and seven in the HVE group were alive 1 week after hepatectomy. Immediately after hepatectomy, portal venous pressure was significantly higher in the control group compared with the HVE group (mean(s.d.) 14·0(1·1) *versus* 8·1(1·0) mmHg; $P < 0·01$). Histological examination of the remnant left lateral lobe demonstrated patchy parenchymal haemorrhage in the control group and normal parenchymal architecture in the HVE group. Peak AST levels were observed on day 1 in both groups and were significantly higher in the control group (mean(s.d.) 182(42) *versus* 67(40) units/l; $P < 0·01$).

Conclusion: In this model, preoperative HVE facilitated interlobar venous collateral formation and minimized the untoward effects of segmental hepatic vein resection. This procedure may obviate the need for hepatic vein reconstruction after cranial partial liver resection including the major hepatic vein.

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Introduction

Hepatectomy provides the only chance of long-term survival for patients with malignant liver tumours. An adequate tumour clearance margin of at least 1 cm is essential if local recurrence is to be avoided[1–3]. In the absence of cirrhosis, an extensive anatomic resection may be required for large tumours or those situated in the central liver parenchyma in order to attain this goal. However, in patients with cirrhosis and a poor functional reserve, this type of resection is often difficult, and every effort should be made to preserve as much functioning liver tissue as possible to prevent postoperative liver failure.

In patients with cirrhosis and a malignant liver tumour in Couinaud's segment VII and/or VIII, cranial partial resection of the right lobe including the right hepatic vein trunk may be indicated to accomplish adequate tumour clearance[4]. However, in this setting, segment VI loses the main outflow tract after the procedure. Based on the results of an experimental study in rats, Nakamura *et al.*[5] reported that congested liver parenchyma resulting from hepatic vein ligation did not function, especially in the early postoperative period. Thus in the case of a small inferior right hepatic vein, they performed hepatic vein reconstruction for the purpose of preserving a drainage vein for segment VI

The Editors have satisfied themselves that all authors have contributed significantly to this publication

following resection of segments VII and VIII[5,6]. Despite a favourable outcome in their limited clinical experience, hepatic vein reconstruction is technically a cumbersome procedure requiring an autogenous vein graft and venous reconstruction after hepatectomy.

Using the dog as a model, it has been demonstrated previously that despite early hydropic changes after ligation of the hepatic vein, the structure of the involved liver segment returns to normal with time because of the later development of intrahepatic venous collaterals[7–10]. Consistent with this notion, numerous venous collaterals around the hepatic vein have been identified by means of retrograde hepatic venography 2 weeks after its segmental ligation in dogs[11]. Based on these findings, it was hypothesized that preoperative hepatic venous embolization (HVE) might minimize the untoward effects of segmental hepatic vein resection. The purpose of this experimental study was to evaluate the efficacy of preoperative HVE in the cranial partial resection of the liver including the major hepatic vein.

Materials and methods

Animals and experimental design

Adult beagles (7–12 kg) of both sexes were used for all experiments. Animal care and all experiments were approved by the Institutional Animal Care and Use Committee, and conformed to guidelines developed by the National Institute of Health for the humane care of animals. The dogs were randomly divided into two groups: group 1 (controls, $n = 8$) and group 2 (HVE pretreated, $n = 8$). Both groups underwent hepatectomy consisting of a cranial partial resection of the left lateral liver lobe and the left hepatic vein. Group 1 received hepatectomy alone, while group 2 underwent HVE 2 weeks before hepatectomy. All dogs were killed with an intravenous overdose of saturated potassium chloride 7 days after hepatectomy.

Hepatic venous embolization

After an overnight fast, the dogs were anaesthetized with intravenous pentobarbital sodium 30 mg/kg and underwent endotracheal intubation. A standard 10-Fr introducer sheath was placed in the right external jugular vein through a small skin incision on the neck. An 8-Fr end-hole occlusion catheter (Boston Scientific Japan, Tokyo, Japan) with a balloon of maximal diameter 27 mm at the distal end was passed via the introducer and advanced under fluoroscopic control to the inferior vena cava until the balloon was just above the hepatic veins. Temporary occlusion of the suprahepatic inferior vena cava was achieved by administration of 7–10 ml half-strength contrast agent into the balloon of the catheter and a venogram was obtained by injection of 20 ml full-strength contrast agent to obtain anatomical information on the hepatic veins. After deflating the balloon, the catheter was advanced under fluoroscopic guidance into the left hepatic vein, and the balloon was positioned as proximally as possible. When the desired position was reached, occlusion was achieved by inflating the balloon with 3–4 ml half-strength contrast agent. With the balloon in the optimal blocking position, the proximal left hepatic vein was embolized by delivering three to four 12-mm fibre-platinum microcoils (Target Therapeutics, Fremont, California, USA). Finally, the balloon catheter was withdrawn into the suprahepatic inferior vena cava and a retrograde hepatic occlusion venogram was performed to confirm complete occlusion of the left hepatic vein with coils (*Fig. 1*). After the procedure, the introducer sheath was removed and haemostasis was achieved with a 5/0 polypropylene suture. The dogs were extubated and allowed to recover.

Cranial partial resection of left lateral liver lobe and left hepatic vein

After an overnight fast, the dogs were anaesthetized as described above, underwent endotracheal intubation and were mechanically ventilated during the operation. A 6-Fr catheter was placed in the left carotid artery for blood pressure and heart rate monitoring and for blood sampling. An 8-Fr balloon occlusion catheter was introduced into the left external jugular vein of dogs that had undergone HVE and retrograde hepatic occlusion venography was per-

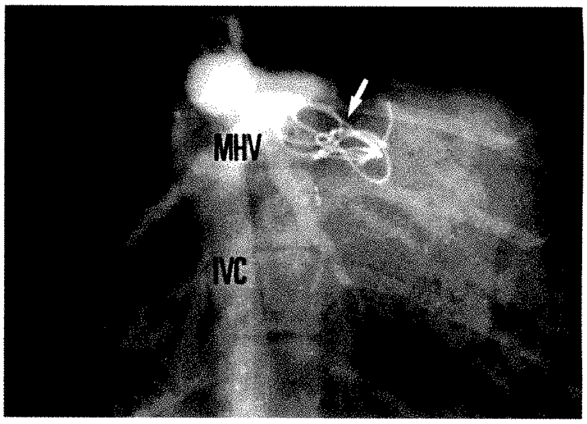


Fig. 1 Retrograde hepatic occlusion venography immediately after hepatic venous embolization with microcoils (arrow) showing complete occlusion of the left hepatic vein trunk. Note the lack of opacification of the left hepatic vein. MHV, middle hepatic vein; IVC, inferior vena cava

formed as above to determine the effect of HVE on the hepatic venous system (*Fig. 2*). The balloon catheter was then changed to a 7-Fr venous catheter through which the dogs in both groups received fluid management with lactated Ringer's solution at 30 ml per kg per h. After a midline laparotomy, the portal vein was cannulated through the pancreaticoduodenal vein for continuous portal venous pressure (PVP) monitoring. The falciform ligament was incised, and the left lateral liver lobe was freed from the peritoneum and the lesser omentum. Subsequently, the confluence of the middle and the left hepatic veins was carefully peeled off from the hepatic parenchyma on the upper hepatic edge. The anterior parenchymal division was made by use of an ultrasonically activated scalpel (Harmonic scalpel®; Ethicon Endo-Surgery, Cincinnati, Ohio, USA) along the outline of the cranial third of the left lateral liver lobe (*Fig. 3*). The dissection was continued until the proximal third of the hepatic vein had been exposed. In the final step, the left hepatic vein was resected approximately 15 mm in length from its root. After control of haemorrhage from the cut surface, a biopsy was taken from the remnant left lateral liver lobe. The catheter in the portal vein was removed 60 min after completion of hepatectomy, and the abdomen was closed.

Evaluation of functional and morphological changes after hepatectomy

The liver specimen obtained from the residual left lateral liver lobe after hepatectomy was sectioned and stained with haematoxylin and eosin. Functional changes were assessed by serial determination of serum aspartate (AST) and alanine (ALT) aminotransferase activities before and after hepatectomy.

Statistical analysis

Data are expressed as mean(s.d.). Statistical analysis was performed with the unpaired Student's t test. $P < 0.05$ was considered statistically significant.

Results

In group 1, two of eight dogs died within 12 h after hepatectomy. Autopsy revealed intra-abdominal haemorrhage with clot on the cut surface of the liver in both animals. The other six control dogs survived 7 days after hepatectomy. Eight dogs in group 2 recovered uneventfully after HVE, and remained healthy until hepatectomy. One of these eight dogs in group 2 died within the first 24 h after hepatectomy. The cause of death could not be determined at autopsy. The remaining seven dogs survived until sacrifice.

Changes in PVP before and after cranial partial resection of the left lateral liver lobe and the left hepatic vein are shown in *Fig. 4*. Mean PVP before hepatectomy was similar in the two groups. However, immediately after resection of the left hepatic vein, PVP increased rapidly in group 1, whereas in group 2 it remained at baseline level. During the first 20 min, the control dogs had significantly higher PVP than those pretreated with HVE.

Macroscopically, the remnant of the left lateral liver lobe

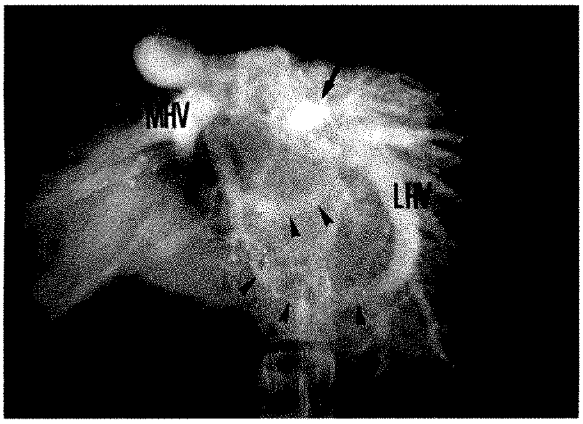


Fig. 2 Retrograde hepatic occlusion venography 2 weeks after hepatic venous embolization showing opacification of the distal left hepatic vein (LHV) through intrahepatic bridging collaterals (arrow heads). An arrow indicates microcoils. MHV, middle hepatic vein

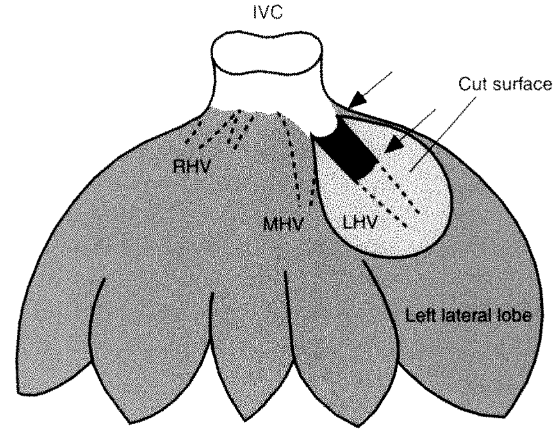


Fig. 3 Schematic drawing of the cranial partial resection of the left lateral liver lobe and the left hepatic vein (LHV). Arrows indicate the resected segment of the LHV. MHV, middle hepatic vein; RHV, right hepatic vein; IVC, inferior vena cava

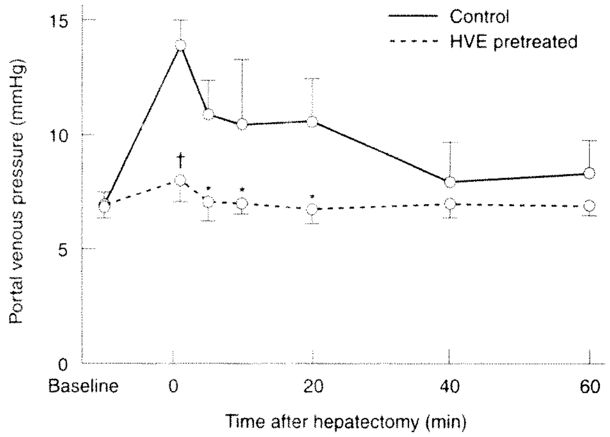


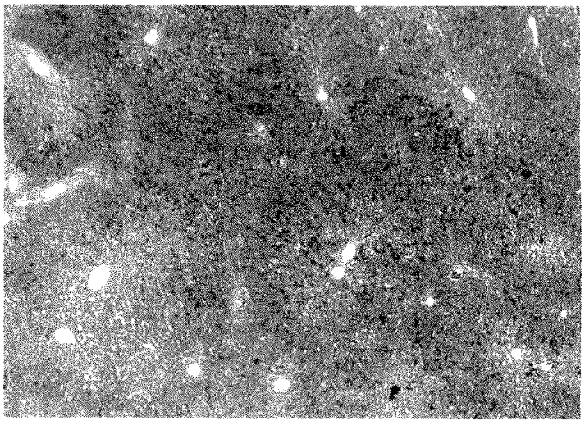
Fig. 4 Changes in portal venous pressure after cranial partial resection of the left lateral liver lobe and the left hepatic vein trunk. Values are mean(s.d.). HVE, hepatic venous embolization. *$P < 0·05$, †$P < 0·01$ *versus* control group (unpaired Student's *t* test)

in group 1 showed distension and a firm consistency immediately after resection of the left hepatic vein; this was not observed in group 2. There was a clear difference between the two groups in the histology of the biopsy specimen taken from the residual portion of the left lateral liver lobe (*Fig. 5*). The most common findings in group 1 were centrilobular congestion and scattered areas of focal parenchymal haemorrhage. In contrast, liver biopsy specimens in group 2 did not show such features. However, in group 2 many central venules were moderately dilated with intimal thickening, and surrounded by a number of venous collaterals in adjacent liver (*Fig. 5c*).

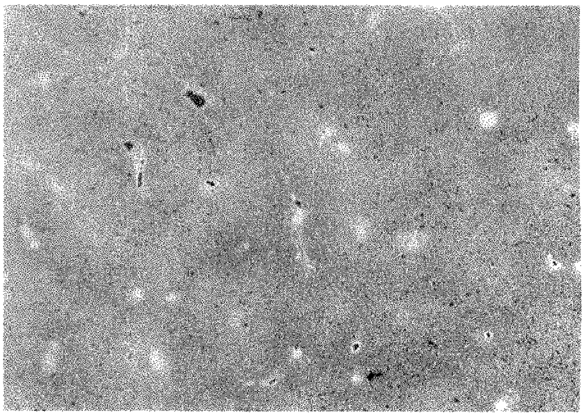
Serial changes in serum AST and ALT activities after hepatectomy are shown in *Fig. 6*. Mean(s.d.) AST levels increased to a maximum of 182(42) units/l in group 1 compared with 67(40) units/l in group 2 at 24 h after operation. Throughout the observation period, the AST levels in group 1 were significantly higher than those in group 2 ($P < 0·01$ on day 1 and day 2; $P < 0·05$ on day 7). ALT levels in each group showed a similar time course to those of AST after hepatectomy, reaching a peak of 306(28) units/l in group 1 and 77(19) units/l in group 2 at 24 h ($P < 0·01$).

Discussion

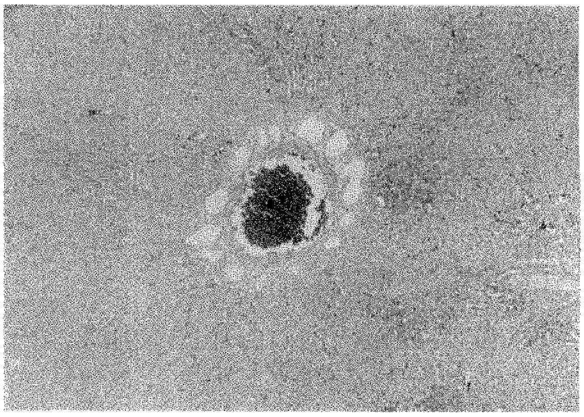
Nakamura *et al.*[5,6] recently advocated hepatectomy combined with hepatic vein reconstruction for the resection of hepatic tumours located at the confluence of the hepatic vein and the inferior vena cava, in order to achieve an adequate tumour clearance margin and to preserve as much



a Control

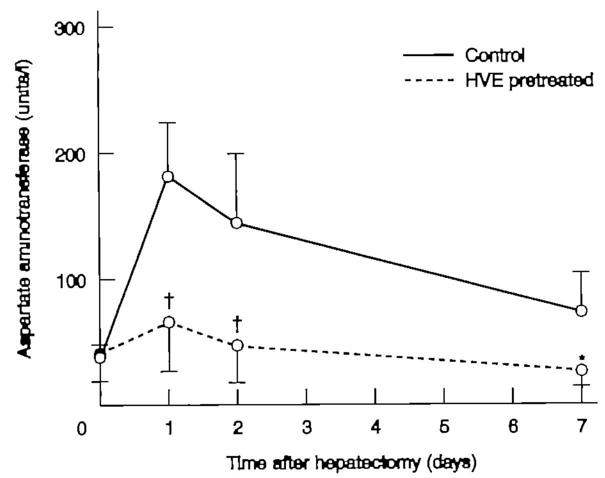


b HVE

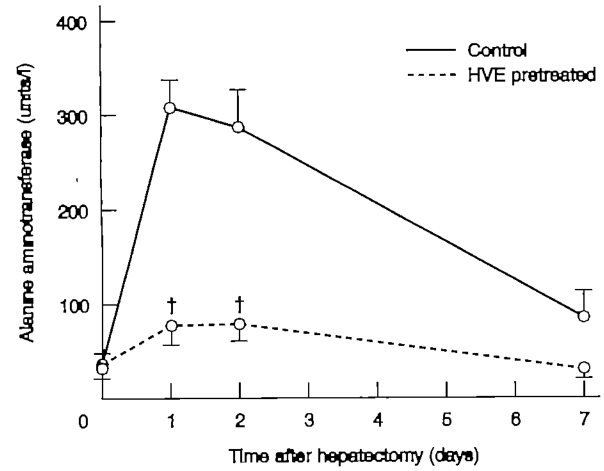


c HVE

Fig. 5 Photomicrographs of the remnant left lateral liver lobe (haematoxylin and eosin stain), showing moderate to severe centrilobular congestion and scattered parenchymal haemorrhage in the control group (**a**; original magnification × 40). Such congestive findings were not seen in the hepatic venous embolization (HVE) group (**b**; original magnification × 40). Note a number of venous collaterals around a central venule in the HVE group (**c**; original magnification × 100)



a Aspartate aminotransferase



b Alanine aminotransferase

Fig. 6 Changes in **a** serum aspartate aminotransferase and **b** serum alanine aminotransferase levels after hepatectomy. Values are mean(s.d.). HVE, hepatic venous embolization. $^{*}P < 0{\cdot}05$, $†P < 0{\cdot}01$ *versus* control group (unpaired Student's *t* test)

normal liver tissue as possible. However, hepatic vein reconstruction is time consuming and not always technically easy to perform. This motivated the authors to investigate a more simple alternative to surgical repair.

This experimental study aimed to evaluate whether HVE stimulates the development of interlobar venous collaterals and thus minimizes the untoward effects of segmental hepatic vein resection after cranial partial resection of the liver. Previous experimental and clinical data indicate that pigs and humans seem to tolerate hepatic vein ligation better than dogs[7,8,10,12,13], implying that the ability of the lobulated canine liver to develop interlobar venous collaterals after segmental hepatic vein occlusion is likely to be lower than that of the human liver. It was therefore assumed that, if they did occur in the canine model, the beneficial effects of preoperative HVE on liver function and morphology could be reproduced in humans.

These experiments have been performed on the left side of the liver. Thus extrapolation of the results into a human scenario may not be straightforward since the clinical situation almost certainly arises in tumours of the right liver and the right hepatic vein. In dogs, however, the right hepatic lobe is much smaller than the left hepatic lobe, which forms a third to nearly a half of the total liver mass. Because of this reversed balance in the canine liver, the current hypothesis was tested on the left side.

Two methods of segmental hepatic vein occlusion have been explored. In a previous study with operative ligation of the left hepatic vein, retrograde hepatic venography at the time of hepatic venous occlusion showed complete lack of opacification of the ligated hepatic venous system[11]. As shown in *Fig. 1*, this finding was reproducible with HVE in the present study and was consistent with anatomical knowledge that the hepatic veins normally have an end vein pattern of distribution, there being no communication between the same or different systems[14–17].

Earlier studies emphasized the need to preserve hepatic venous drainage for the remnant liver during hepatectomy to prevent postoperative liver congestion and malfunction[14,15]. However, a number of investigators have subsequently studied the pathophysiological consequences of segmental hepatic vein occlusion in animal models. The data clearly indicated that the outcome of segmental hepatic vein ligation is different from that of subtotal or total hepatic vein occlusion, and that necrosis or atrophy of the liver does not necessarily occur if the involved liver segment is limited to a certain extent[7–10,12]. In dogs, the safe limit for segmental occlusion of the hepatic vein is in the range of 50–55 per cent of the total liver mass[7,8,10]. In support of these findings, all dogs in this study tolerated segmental embolization of the left hepatic vein, which normally provides venous drainage of approximately 40 per cent of the whole liver mass.

Previous reports have identified two major mechanisms by which segmental hepatic vein occlusion can be tolerated[8–10,12,18–20]. In the early stage, retrograde flow in the portal vein from the affected liver segment to an unaffected segment functions as a means of haemodynamic compensation[18–20]. In the present study the control dogs showed an immediate increase in PVP after cranial partial resection of the left lateral lobe including the left hepatic vein trunk. Interestingly, the PVP gradually returned to baseline level during the 60-min observation period. Similar changes in

PVP were seen after segmental hepatic vein ligation[11]. In addition, both studies demonstrated the absence of venous anastomoses between the radicles of the hepatic vein system at the time of hepatic venous occlusion by retrograde hepatic venography, suggesting that the conversion of the portal tract to an outflow channel is rapidly established within an hour, and has an important role in maintaining venous return from the affected segment in the acute stage of segmental hepatic vein occlusion.

Another compensatory mechanism is intrahepatic venous collateral formation in the later stage of segmental hepatic vein occlusion. Previous studies have shown that interlobar and interlobular collaterals develop between the patent and occluded hepatic veins after hepatic vein ligation[8–12]. In this study, bridging collaterals were clearly visualized at retrograde hepatic occlusion venography performed 2 weeks after HVE (*Fig. 2*). In addition, the liver in the HVE-pretreated dogs was not congested, and many thin-walled venous collaterals were seen around the central venule on microscopy. Similarly, Winternitz[7] ligated a single hepatic vein in a dog, and found a normal liver weeks later. Using pigs as a model, Kaman and Cerveny[12] found that the affected liver segment recovered from congestion morphologically and functionally, as early as 7 days after segmental hepatic vein ligation. Thus adequate venous collaterals develop rapidly, and are established within 2 weeks in large animals, irrespective of the method of segmental hepatic vein occlusion.

HVE-pretreated dogs showed less impairment of liver function (serum AST and ALT concentrations) after cranial partial resection of the left lateral liver lobe including the left hepatic vein. These findings indicate that the intrahepatic venous collaterals can function as the efferent channel and contribute, at least in part, to the prevention of postoperative congestion and injury of the affected liver segment in dogs.

It is important to note that PVP was raised after hepatectomy in the controls for less than 1 h, whereas changes in AST and ALT and histological changes were longer lasting. Parker[21] postulated that in a lobule in which the hepatic artery is the afferent and the portal vein the efferent channel, blood perfusion would be profoundly reduced in the centrilobular region. This mechanism of ischaemic injury might be an additional factor in the control dogs until adequate venous collateralization is established after hepatectomy.

These experiments were performed in animals with normal livers. The question remains of whether the benefit of preoperative HVE is reproducible in cirrhotic liver. A previous anatomical study has shown that extensive anastomoses develop between portal branches and hepatic veins located in the fibrous septum in human cirrhotic livers[22]. It may be speculated that these internal anastomoses could act as efferent channels, and eventually contribute to interlobar collateral formation after segmental hepatic vein occlusion.

One potential concern about applying HVE clinically is the risk of dislodgement of embolic material into the right atrium. To avoid this complication, the ostium of the left hepatic vein was occluded with a balloon-tipped catheter when the coils were released into the hepatic vein. With this protection the coils were placed successfully in the desired position in all but one dog, in which one of the coils was directed into the right atrium. Further technical modifications will be required to avoid this critical complication of HVE before its clinical application.

In conclusion, this study demonstrates that HVE minimizes the untoward effects on liver morphology and function in the remnant segment after cranial partial resection of the canine liver including the major hepatic vein trunk. This approach may obviate the need for hepatic vein reconstruction in the clinical setting.

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Effect of chronic renal failure on mortality rate following arterial reconstruction

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Background: There is some evidence that patients with renal failure who have arterial procedures may have a poor outcome. This study compared the hospital mortality rate of arterial surgery in patients with chronic renal failure and those with normal renal function.

Methods: A consecutive series of 1718 patients undergoing arterial reconstructive surgery (excluding amputation) was entered prospectively on to a computerized database. Chronic renal failure was defined as a serum creatinine level over 400 µmol/l, or dialysis (either peritoneal or haemodialysis), or a successful renal transplant. Mortality was assessed at 30 days or in hospital.

Results: There were 69 patients (4·0 per cent) who were defined as having chronic renal failure. The mortality rate in this group was 23 per cent (16 patients) compared with 7·3 per cent (120 patients) of the 1649 patients without renal failure. The mortality rate was highest in patients undergoing urgent or emergency surgery and in those undergoing reconstruction for lower limb occlusive disease. The main causes of death were related to the cardiovascular system.

Conclusion: Patients with chronic renal failure undergoing arterial surgery have a poor outcome compared with those with normal renal function.

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Introduction

The majority of patients who undergo arterial reconstruction for peripheral vascular disease have atherosclerosis. An increasing and significant number of patients with end-stage renal disease also develop occlusive or aneurysm arterial disease that requires surgery.

There is a complex interrelationship between end-stage renal disease, atherosclerosis and vascular intervention. There is an increasing awareness that end-stage renal disease may be secondary to atherosclerotic renal artery stenosis and that treatment of this may delay or reduce the requirement for dialysis[1,2]. Patients with end-stage renal disease are more likely to develop accelerated atherosclerosis necessitating vascular intervention; atherosclerosis may affect the coronary circulation causing cardiac failure. End-stage renal disease has been shown to increase plasma levels of fibrinogen, cholesterol, lipoprotein (a) and homocysteine, which may also encourage the development of atherosclerosis[3–5]. Secondary hyperparathyroidism and hypertension have been shown to accelerate the effects of atherosclerosis[6]. Finally, patients with peripheral vascular disease may have unsuspected renal artery stenosis[7,8], which is a strong independent predictor of 4-year survival[9].

Previous studies have shown that patients with chronic renal failure have three times the risk of myocardial infarction compared with the general population[10]. Cardiovascular disease accounts for nearly half the deaths in patients with end-stage renal disease[11]. Interestingly, peripheral vascular disease is a marker of poor outcome in patients with end-stage renal disease[12,13]. Patients with end-stage renal disease who undergo arterial surgery have an increased operative mortality rate and poor long-term survival[14,15]. In one study on lower limb arterial bypass, the preoperative creatinine level predicted limb salvage and patient survival[15].

The present study was undertaken in a consecutive series of patients who had arterial surgery and was designed to compare the hospital mortality rate in patients with chronic renal failure and patients with normal renal function.

Patients and methods

A consecutive series of 1718 patients who had arterial surgery (excluding amputation) was entered prospectively on to a computerized database over an 8-year interval. Preoperative risk factors recorded were smoking, diabetes, hypertension, history of myocardial infarction, coronary revascularization, angina, history of stroke, hyperlipidaemia, chronic renal failure, myxoedema and gout. The hospital is a regional renal unit and accepts referrals from the whole of south-east England. Patients with renal failure were those with a serum creatinine level over 400 μmol/l ($n = 56$), patients who received either peritoneal or haemodialysis ($n = 7$) or those who had undergone successful renal transplantation ($n = 6$). The value of a serum creatinine concentration greater than 400 μmol/l was chosen arbitrarily since there is no absolute value that defines renal failure. The study endpoint was death assessed at 30 days or in hospital if the patient had not left hospital following surgery. Differences between the two groups of patients were assessed by χ^2 analysis and Mann–Whitney test where appropriate. $P < 0{\cdot}05$ was considered significant.

Results

There were 69 patients with chronic renal failure, 4·0 per cent of the study group. There were no differences between the two groups with regard to age, sex and indication for surgery. Significantly more patients with renal failure had hypertension, hyperlipidaemia and gout (*Table 1*). There was a greater than threefold increase in mortality rate in the patients with chronic renal failure (23 per cent) compared with those with normal renal function (7·3 per cent); the rate was highest in those who needed urgent or emergency surgery (*Table 2*). Although there was a higher overall mortality rate in patients with renal failure who had aortic aneurysm surgery, this did not achieve statistical significance. There were too few patients to analyse elective and emergency aortic surgery separately. Patients with chronic renal failure who had lower limb arterial reconstruction had a fivefold increase in mortality rate.

There were 120 deaths in the patients with normal renal function, 43 (35·8 per cent) in patients who had an elective operation and 77 (64·2 per cent) in those who underwent emergency or urgent surgery (*Table 3*). In the patients with renal failure, there were 16 deaths, nine in patients who had elective and seven in those who had emergency or urgent

Table 1 Risk factors in 1718 patients who had arterial surgery

	Renal failure (n = 69)	Normal renal function (n = 1649)
Smoking	48 (70)	1270 (77·0)
Hypertension	51 (74)	709 (43·0)*
Diabetes	12 (17)	182 (11·0)
Myocardial infarction	17 (25)	280 (17·0)
Coronary revascularization	8 (12)	181 (11·0)
Angina	7 (10)	231 (14·0)
Stroke	1 (1)	33 (2·0)
Gout	11 (16)	66 (4·0)*
Myxoedema	4 (6)	49 (3·0)
Hyperlipidaemia	20 (29)	49 (3·0)*

Values in parentheses are percentages. $^*P < 0{\cdot}01$ *versus* renal failure (Mann–Whitney U test)

Table 2 Mortality rates in patients who had arterial surgery

	Renal failure		Normal renal function	
	n	Deaths	n	Deaths
All elective operations	51	9 (18)	1103	43 (3·9)*
Urgent and emergency operations	18	7 (39)	546	77 (14·1)*
All operations	69	16 (23)	1649	120 (7·3)*
Aneurysm repair	35	8 (23)	391	54 (13·8)
Infrainguinal bypass	14	5 (36)	387	25 (6·5)*

Values in parentheses are percentages. $^*P < 0{\cdot}01$ *versus* renal failure (χ^2 test)

Table 3 Causes of death

	Renal failure (n = 69)	Normal renal function (n = 1649)
Myocardial infarction	7 (10)	26 (1·6)*
Multiple sequential organ failure	3 (4)	21 (1·3)
Stroke	1 (1)	10 (0·6)
Mesenteric thrombosis	1 (1)	10 (0·6)
Paraplegia	2 (3)	1 (0·1)
Respiratory failure	1 (1)	5 (0·3)
Pneumonia	1 (1)	0 (0)
Failure to control haemorrhage	0 (0)	9 (0·5)
Cardiac failure	0 (0)	7 (0·4)
Coagulopathy	0 (0)	7 (0·4)
Ischaemic legs	0 (0)	6 (0·4)
Uncontrolled haemorrhage	0 (0)	6 (0·4)
Unknown	0 (0)	4 (0·2)
Pulmonary embolism	0 (0)	3 (0·2)
Carcinomatosis	0 (0)	2 (0·1)
Aspiration pneumonia	0 (0)	1 (0·1)
Renal failure	0 (0)	1 (0·1)
Sepsis	0 (0)	1 (0·1)
Total	16	120

Values in parentheses are percentages. $^*P = 0{\cdot}05$ *versus* renal failure (Mann–Whitney U test) surgery. The majority of deaths were related to the cardiovascular system; myocardial infarction was the commonest cause followed by multiple sequential system failure. There was a significant increase in the mortality rate from myocardial infarction ($P = 0.05$) in patients with renal failure.

Discussion

The number of patients presenting with arterial disease and coexisting renal failure is increasing. Patients with end-stage renal disease have a high risk of death when undergoing arterial reconstruction for lower limb occlusive disease[15–20]. Seeger *et al.*[15] found renal failure to be most commonly associated with a fatal outcome in their series of 210 patients undergoing infrainguinal bypass. Similarly, Peltonen *et al.*[16] in a small series of 35 patients with impaired renal function noted a dismal outcome in those who required dialysis; no patient survived with salvaged legs 4 months after revascularization. It was concluded that revascularization is seldom indicated in patients on dialysis.

In an analysis of 77 patients with end-stage renal disease undergoing either amputation or leg revascularization, Simsir *et al.*[17] found limb salvage in survivors of 67 per cent at 1 year, with overall 1-year survival of 72 per cent after both operations. It was suggested that overall survival could be improved by more liberal use of primary amputation in patients with end-stage renal disease and critical limb ischaemia. Baele *et al.*[18], however, concluded that an acceptable level of limb salvage may be achieved in properly selected patients. Hakaim *et al.*[19] reported no difference in perioperative mortality rate between patients with end-stage renal disease and diabetes and patients with diabetes alone. Leers *et al.*[21] described 34 patients with end-stage renal disease who had pedal bypass with a survival rate of 64 per cent at 1 year and 52 per cent at 2 years. These single-centre studies comprised small numbers so that type 2 errors cannot be excluded, but it seems reasonable to conclude that the mortality rate is increased in patients with end-stage renal disease undergoing infrainguinal bypass.

In contrast, two studies have shown that, although long-term survival is poor, aortic aneurysm repair can be performed with low in-hospital mortality rates in patients with chronic renal failure[14,22]. In the first of these, 187 patients underwent elective aortic aneurysm repair with a perioperative mortality rate of 5·9 per cent. Of the 176 survivors, 70 (39·8 per cent) died during the 4-year follow-up. Both age and chronic renal failure were predictive variables for late outcome. The second study compared the mortality rate in three groups of patients considered for abdominal aortic aneurysm surgery. There was no significant difference in mortality rate in patients with normal or abnormal renal function who had elective surgery. Seven patients in a group of 18 with renal dysfunction who were unfit for surgery died from ruptured aneurysm.

The present study has shown that the combination of atherosclerosis and the requirement for arterial reconstruction was associated with a threefold increase in mortality rate in patients with end-stage renal disease. The majority of these patients died from cardiovascular causes, and the combination of renal failure and the need for arterial surgery seemed to be a strong marker for cardiac disease. Hypertension, hyperlipidaemia and gout were significantly more common in these patients and were likely to be important long-term contributory factors to coronary and peripheral arterial disease. The majority of patients with renal failure were assessed and treated by a renal physician before surgery, but specific cardiac tests such as echocardiography and thallium scanning were not performed routinely, nor were these patients assessed routinely by a cardiologist. The value of assessment of cardiac function before peripheral arterial intervention has been questioned[23], but it might be important in patients with renal failure. Lee *et al.*[24] have derived a simple index for prediction of cardiac risk in patients undergoing major non-cardiac surgery. Some 4315 patients aged over 50 years were studied; six independent predictors were identified: high-risk surgery, history of ischaemic heart disease, history of congestive cardiac failure, history of cerebrovascular disease, preoperative treatment with insulin and preoperative serum creatinine greater than 2·0 mg/dl (176·8 µmol/l). However, the study included only patients undergoing elective surgery. In the current study 32·8 per cent of the patients presented with emergency or urgent problems, which prevented a full preoperative assessment and appropriate cardiac intervention.

The cost-effectiveness of cardiac procedures before vascular reconstruction needs to be investigated in patients with renal dysfunction who have a limited life expectancy. Nevertheless, correction of significant coronary disease could improve the overall prognosis of patients with end-stage renal disease who need vascular surgery.

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Original article

Value of isotope lymphography in the diagnosis of lymphoedema of the leg

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Background: Isotope lymphography has largely replaced contrast lymphography in the diagnosis of lymphoedema. Its accuracy has only been assessed in small studies and it is not known if it can identify patients with a proximal lymphatic obstruction who may be suitable for lymphatic bypass surgery.

Methods: Three hundred and ninety-five patients suspected to have lymphoedema were investigated by isotope lymphography between 1985 and 1995. Contrast lymphography was also carried out in 29 of these patients because the isotope results were thought to be misleading, or because lymphatic bypass surgery was being considered.

Results: In the 29 patients who had both investigations isotope lymphography detected 20 of 24 abnormal lymphatic systems. Four legs with obstructed groin lymphatics were reported as normal. Two legs with normal contrast lymphograms were erroneously diagnosed as having lymphoedema in the isotope study. Detectable groin nodes on the scintigrams were indicative of either normal lymphatics or proximal lymphatic obstruction. An increase in isotope uptake over 30–60 min of less than 50 per cent, or a total absence of isotope within groin nodes, was a sensitive indicator that patients were unsuitable for lymphatic bypass surgery.

Conclusion: Isotope lymphography is a moderately sensitive test for lymphoedema, which will mistakenly classify some normal legs as lymphoedematous. It will usually correctly identify patients who are suitable for lymphatic bypass surgery.

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Introduction

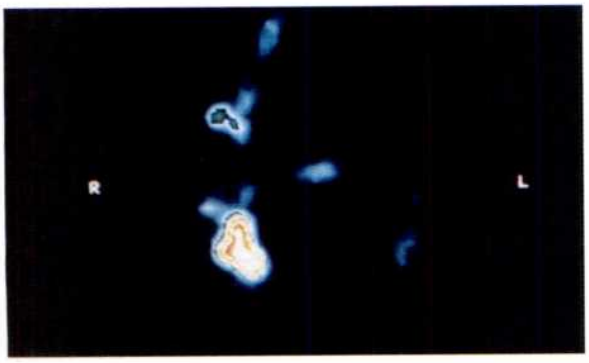
Before 1985 contrast lymphography was always used in St Thomas' Hospital to confirm the clinical diagnosis of lymphoedema. The introduction of isotope lymphography[1] (also known as lymphoscintigraphy) made contrast lymphography largely unnecessary, because it was simple, relatively inexpensive, and avoided general anaesthesia and admission to hospital. There are no reports of serious adverse events after isotope lymphography, but there is a theoretical risk of teratogenesis during pregnancy.

Isotope lymphography has been reported to have good sensitivity and specificity in diagnosing lymphoedema in patients with swollen legs[1–6]. A few studies have suggested that isotope lymphography can differentiate the different patterns of lymphoedema[4], including the degree of lymphatic obstruction present[3]. These studies, however, relied on subjective interpretation of isotope lymphograms and are therefore of doubtful validity. By comparison, contrast lymphography not only confirms the diagnosis of lymphoedema but also reveals the exact position of the lymphatic obstruction. The identification of patients with obstructed lymphatics in the ilioinguinal region is important, as obstruction at this level may sometimes be successfully bypassed using the enteromesenteric bridge operation developed by Kinmonth[7–9] or other microanastomotic techniques. The purpose of this study was to determine the accuracy of isotope lymphography in determining the diagnosis of lymphoedema, and the presence and level of proximal lymphatic obstruction in the leg.

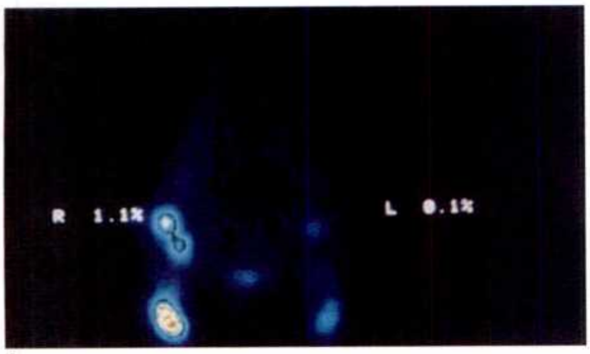
Patients and methods

Isotope lymphography (*Fig. 1*)

Isotope lymphography was performed in the Department of Nuclear Medicine. Some 0·25 ml ^{99m}Tc-radiolabelled rhenium sulphur colloid (75 MBq) was injected into the



a 30 min



b 60 min

Fig. 1 Radioisotope scans of the pelvis of a 20-year-old-woman complaining of a swollen left leg taken at **a** 30 min and **b** 60 min. At 30 min there is minimal uptake on the left; by 60 min uptake is 0·1 per cent, confirming the clinical findings of lymphoedema

second or third subcutaneous web spaces of both feet. The legs and pelvis were scanned, using an IGE γ camera (General Electric Medical Systems, Slough, UK) with a general purpose collimator, 30 and 60 min after the injection. For the first 30 min the patients sat at rest. During the second 30 min, they were asked to get up and walk to stimulate lymphatic return. The quantity of isotope taken up in the groin region (the inguinal and external iliac lymph glands) was expressed as a percentage of the initial dose injected.

The diagnosis of lymphoedema was accepted if less than 0·3 per cent of the isotope reached the groin nodes by 30 min[1]. The study was considered to be equivocal if the uptake was between 0·3 and 0·6 per cent, but probably indicative of lymphoedema. An uptake greater than 0·6 per cent suggested that the leg had normal lymphatics, although an isotope uptake of greater than 1·5 per cent at 30 min was thought to indicate the presence of a venous disorder[1].

Contrast lymphography (*Fig. 2*)

Patients were admitted to hospital 24 h before contrast lymphography for bed rest and leg elevation to reduce the oedema. Under general anaesthesia the lymphatic vessels were outlined by injecting Patent Blue Violet into the interdigital web spaces[5]. Through a short transverse incision on the dorsum of the foot, the lymphatics were dissected out using an operating microscope, before being cannulated and slowly infused with ultra fluid lipiodol using a specially designed pump. Radiographs were taken of the whole leg until the contrast passed the sacroiliac joint or until 7·5 ml lipiodol had been infused into each leg. Radiographs of the groin, pelvis and abdomen were taken the following day to review the contrast filling and the appearance of the lymph nodes.

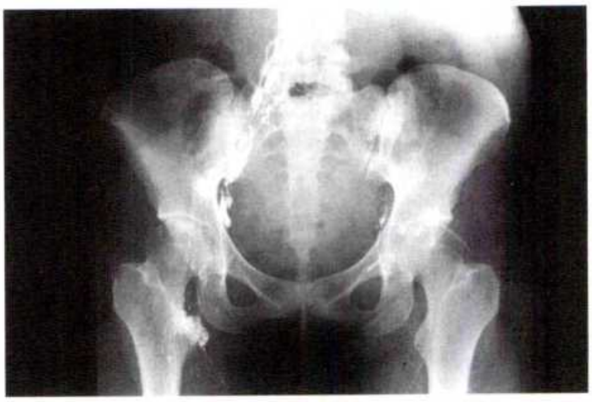


Fig. 2 Contrast lymphogram. The lymphatics of the right leg are normal. The left thigh has a single visible lymphatic vessel passing to hypoplastic groin nodes, with no evidence of proximal flow. The patient has a lymphatic obstruction at the groin, but is unsuitable for enteromesenteric bridge surgery because of obliteration of the lymphatic vessels in the thigh

Comparison of isotope lymphography and contrast lymphography

The results of the isotope lymphograms performed between 1985 and 1995 were reviewed. Thirty legs in 29 patients investigated by both contrast and isotopic investigations were compared. The isotope lymphograms were reviewed to determine the percentage of isotope uptake at the groin at 30 and 60 min, and the presence or absence of visible lymph nodes in the groin and above. Unfortunately, because of protocol violations, the 60-min uptake was measured in only 25 of the 30 legs. The contrast lymphograms were reviewed to determine the number and appearance of the lymphatic channels in the thigh and lower leg, and the presence of lipiodol in the inguinal, iliac and para-aortic lymph nodes. Failure of contrast to progress through the inguinal lymph nodes into the upper iliac and para-aortic nodes was regarded as clear-cut evidence of proximal lymphatic obstruction.

Results

Value of isotope lymphography for confirming a clinical diagnosis of lymphoedema

Three hundred and ninety-five patients seen over 10 years with swollen legs, suspected clinically to have lymphoedema, were investigated by isotope lymphography. Lymphoedema was confirmed in one or both limbs of 347 patients by an isotope lymphogram result within the diagnostic range. Twenty-four of these patients were considered to have a secondary cause for the lymphoedema: 13 had previously undergone surgery to the groin or pelvic lymph nodes, three had severe injuries of the leg or groin, three had previous treatment with radiotherapy, three had a known malignancy and two were found to have high titres of filarial antibodies. The remaining 323 patients had a diagnosis of primary lymphoedema.

Forty-eight patients had a normal or 'venous' isotope lymphogram; 27 (all women) were thought to have idiopathic cyclical oedema, eight had varicose veins, seven had lipodystrophy, three had post-thrombotic legs, two had iliac vein compression and one patient was found to have an extensive venous angioma on magnetic resonance imaging.

Comparison of isotope lymphography at 30 min and contrast lymphography in the diagnosis of lymphoedema

Thirty swollen legs in 29 patients had contrast lymphography because the results of the isotope lymphogram were suspected to be incorrect or because lymphatic bypass surgery was being considered. The two investigations concurred in 24 legs: 20 had lymphoedema and four were normal. The two tests disagreed in six legs. In two the isotope lymphogram was abnormal (uptake less than 0·6 per cent) but the contrast lymphogram was normal. One of these legs may have had an intradermal injection of isotope because although the groin uptake at 30 min was less than 0·6 per cent, it was in the normal range by 60 min. The other leg, which was obese, had an isotope uptake only fractionally below the normal range. In four legs the isotope lymphogram was normal but the contrast lymphogram was abnormal, revealing proximal (ilioinguinal) node obstruction.

The sensitivity of the isotope studies at 30 min compared with contrast lymphography in detecting an abnormal lymphatic system was 83 per cent (20 of 24) and the specificity 67 per cent (four of six). Limbs with proximal obstruction had the greatest risk of being diagnosed incorrectly because the uptake at the groin at 30 min was sometimes within the normal range.

Table 1 Diagnosis of causes of lymphoedema related to the two investigations and the visibility of groin nodes

	Isotope lymphography	
	Groin nodes visible	Groin nodes not visible
Diagnosis based on contrast lymphography		
Normal	6	0
Proximal obstruction	10	2
Numerical hypoplasia	1	2
Megalymphatics	0	2

Ability of isotope lymphography at 30 min to display the inguinal lymph nodes compared with contrast lymphography

The two investigations agreed in 24 legs; the groin lymph nodes were visible in 17 limbs and invisible in seven. In six legs the isotope lymphogram failed to demonstrate groin nodes that were filled on the contrast lymphogram. There were no occasions on which nodes were seen on the isotope lymphogram but not on the contrast lymphogram. The sensitivity of the isotope lymphogram at 30 min at revealing lymph nodes shown on contrast lymphography was 74 per cent (17 of 23) but the specificity was only 54 per cent (seven of 13).

The final diagnosis of the 17 limbs in which the isotope lymphogram demonstrated groin node uptake is shown in *Table 1*. It is notable that two of the six legs with no isotope uptake in the groin node had proximal obstruction (and were subsequently found to be suitable for bypass surgery after contrast lymphography). Six legs with an uptake below 0·3 per cent (diagnostic of lymphoedema) and two with an uptake in the 0·3–0·6 per cent (equivocal) range also had proximal obstruction, confirming the relative inability of the 30-min isotope scan to detect proximal lymphatic obstruction.

Significance of a change in uptake of isotope between the 30- and 60-min isotope lymphograms as an indicator of proximal obstruction

The inability of the 30-min scan reliably to detect proximal obstruction led to an examination of the value of measuring the change in uptake between the 30- and 60-min scans. An estimation of the isotope uptake at 60 min was performed in only 26 of the 30 legs assessed by the two lymphography techniques. The percentage increase in isotope uptake in the groin nodes between 30 and 60 min was greater than 100 per cent in 14 legs, between 50 and 99 per cent in seven

Table 2 Relationship between percentage increase in isotope uptake in the groin between 30 and 60 min and the diagnosis based on contrast lymphography

Percentage increase in groin uptake between 30 and 60 min on isotope lymphography	Contrast lymphography diagnosis			
	Proximal obstruction	Distal obliteration	Megalymphatics	Normal lymphatics
> 100	8	1	1	4
50–99	3	2	1	1
25–49	–	1	–	3
< 24	1	–	–	–

legs, between 25 and 49 per cent in four legs and less than 24 per cent in one leg. The corresponding diagnoses are summarized in *Table 2*.

Twelve of the 26 legs had evidence of proximal obstruction on contrast lymphography. In eight the uptake of isotope in the inguinal nodes increased by more than 100 per cent, and in three it had increased between 50 and 99 per cent. The only leg with proximal obstruction that did not show an increase of greater than 50 per cent also had inadequate distal lymphatics. Seven of the 11 legs with proximal obstruction and an increase in isotope concentration greater than 50 per cent had normal lymphatics in the thigh, and four had a reduction in the number of thigh lymphatics. Three legs with distal obliteration had a percentage isotope increase of greater than 50 per cent, but all had very low uptakes at 30 min (0·04, 0·03 and 0·02 per cent), and none increased above 0·1 per cent after 60 min.

Discussion

Isotope lymphography is an effective method for identifying abnormal lymphatics in the leg, and it appears to misdiagnose very few cases of lymphoedema[10]. The absence of visible lymph nodes on isotope lymphography either indicates peripheral lymphatic obliteration or the inability of the vessels to transport lymph up the limb through incompetent megalymphatics. Patients with these conditions are not suitable for lymphatic bypass surgery, and in these circumstances lymphoscintigraphy is a good sceening test. It is not very specific, however, because the inguinal lymph nodes of some patients with lymphatic obstruction at the groin and some with normal lymphatics may not be visualized by 30 min after the injection of isotope into the foot. An ilioinguinal node uptake of less than 0·3 per cent of the injected isotope by 30 min reliably indicates the presence of a lymphatic abnormality but does not exclude the possibility that the cause might be proximal obstruction. The low specificity in these patients probably reflects the fact that isotope lymphography identifies some normal legs as being lymphoedematous. Another reason for this may be the inadvertent intradermal injection of isotope, which might have occurred in one patient who had very low uptake at 30 min that increased rapidly to normal levels after an hour. It is also possible that isotope lymphography, which is a physiological test, can detect an early functional abnormality of peripheral lymph reabsorption, while the main lymph trunks of the limb, visualized by contrast lymphography, are still normal. The routine use of both investigations was abandoned in 1985 after a study showed good concordance[1]. Since then contrast studies have been reserved for patients with equivocal or unexpected results from an isotope study. The true sensitivity and specificity of isotope lymphography cannot be addressed by the present study, but it is now accepted as a first-line investigation[10].

The presence of discernable groin lymph nodes on isotope lymphography may indicate either normal lymphatics or lymphatics that are obstructed above the groin. The change in the percentage isotope uptake between the 30 and 60-min scans proved useful as an indicator of how much lymph is reaching the groin. If an increase in radioactivity in the inguinal region of more than 50 per cent between the 30- and 60-min scans, together with a 60-min scan showing an uptake greater than 1·0 per cent, was used to indicate the need for contrast lymphography, three limbs with obstruction would have been missed and no patient with distal obliteration would have been investigated unnecessarily. If an increase in radioactivity of greater than 50 per cent was used as the sole criterion, one leg with obstruction would have been missed and three patients with distal obliteration would have been subjected to contrast lymphography.

An increase in the percentage uptake of isotope in the groin nodes at 60 min of more than 50 per cent of the uptake at 30 min excludes the majority of patients with absent, obliterated or a severely reduced number of lymphatics, even when there is a coexisting proximal obstruction. This includes some patients with ilioinguinal obstruction complicated by lymphatic 'die-back' of the collecting lymphatics in the limb (progressive distal obliteration of chronically obstructed lymphatics), although this does not matter as this type of disease is unsuitable for lymphatic bypass surgery[11]. All but one of the patients with proximal obstruction and an isotope increase greater than 50 per cent had between four and 15 lymphatic vessels reaching the groin nodes. Lymphatic bypass surgery may be considered in this situation, although its feasibility must be confirmed by contrast lymphography. Contrast lymphography is also a helpful investigation in patients in whom the clinical diagnosis of lymphoedema remains a strong possibility despite an apparently normal isotope study. This is particularly true if there is oedema of the upper two-thirds of the leg, especially the thigh, with sparing of the foot. This clinical picture is strongly suggestive of lymphatic obstruction at the groin. As with all investigations, a decision on further investigation and management should not be based solely on the results of a single study but must be considered in combination with the history and physical signs.

Isotope lymphography can confirm a clinical diagnosis and indicate the likelihood of conservative or surgical treatment in most patients. When the results of the isotope lymphogram suggest proximal obstruction or do not fit the clinical picture, contrast lymphography may still help to obtain a definitive diagnosis.

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Original article

Fissurectomy and isosorbide dinitrate for chronic fissure *in ano* not responding to conservative treatment

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Background: Although lateral sphincterotomy heals chronic fissure *in ano* in over 90 per cent of cases it is a surgical technique with inherent complications. To avoid such complications, chronic fissure *in ano* was treated by fissurectomy in this study. To enhance postoperative tissue perfusion allowing stable wound healing, fissurectomy was combined with temporary chemical sphincterotomy by a nitric oxide donor cream.

Methods: Seventeen consecutive patients (ten women) with chronic fissure *in ano* not responding to conservative management underwent diathermy fissurectomy. After operation patients used a 1 per cent isosorbide dinitrate cream. Postoperative follow-up continued until wounds had healed, at which time anal endosonography was performed. A telephone inquiry into fissure recurrence and continence status was made.

Results: Seventeen patients underwent fissurectomy, without postoperative complications. All wounds had healed within 10 weeks. No fissure recurrence was seen after a median follow-up of 29 months. Histopathology showed non-specific scar tissue without signs of internal anal sphincter fibrosis. Postoperative endosonography showed no evidence of new internal sphincter defects.

Conclusion: In the treatment of chronic anal fissure not responding to chemical sphincterotomy with nitric oxide donors, fissurectomy in combination with isosorbide dinitrate cream may be a sphincter-sparing surgical technique.

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Introduction

Despite the advent of nitric oxide donors, chronic fissure *in ano* frequently needs surgical treatment. Lateral internal sphincterotomy is an effective treatment but it is not without the potential for long-term complications. Incontinence to flatus and faecal soiling are distressing complications of sphincterotomy that may occur in up to 35 per cent of patients[1,2]. Surgical techniques that preserve the anal sphincters and that do not create gutter defects should reduce the possibility of postoperative faecal incontinence. This study was designed to study the hypothesis that chronic anal fissures unresponsive to conservative treatment may be regarded as unstable scar tissue. The combination of fissure excision to create a fresh surgical wound, and use of nitric oxide donors to improve tissue perfusion through a reversible chemical sphincterotomy might then allow stable wound healing.

Patients and methods

Seventeen consecutive patients (ten women) with a mean age of 46 (range 29–78) years with chronic painful anal fissures consented to diathermy fissurectomy and postoperative isosorbide dinitrate (IDN) treatment. All patients had failed standard conservative treatment that consisted of a stool bulking agent and topical 1 per cent IDN cream for a mean of 17 (range 13–20) weeks. IDN treatment had not failed because of side-effects. Fissures were painful on palpation and were located in the posterior midline in 15 patients and anterior midline in two female patients. All patients had sentinel piles or skin tags. Eight of ten women were multiparous. All patients had had classical symptoms of chronic anal fissure for more than 4 months. One patient had previously had a lateral internal sphincterotomy but the fissure recurred 3 years later.

Fissurectomy

Two days before operation patients started to take an oral stool bulking agent twice daily. The operation was performed by a single surgeon, with the patient in a prone jack-knife position. No anal dilatation was used, vascular pedicles were coagulated and complete excision of the fissure, including its base, was performed with a lateral margin of approximately 5 mm of healthy mucosa. The wound was left open. No anal tampons were used. Wound edges were infiltrated with 8–10 ml 0·5 per cent bupivacaine and adrenaline 1 : 200 000. After operation patients commenced topical 1 per cent IDN cream four to six times daily. Outpatient visits were scheduled 4, 14 and 42 days after operation. Patients were told that they would be contacted subsequently by telephone regarding symptoms and postoperative continence.

Histopathology

Surgically excised specimens were fixed in a 4 per cent buffered formalin solution. The tissue was sliced into 3-mm blocks. All blocks were routinely embedded in paraffin. Sections 5 μm thick were stained with haematoxylin and eosin. To distinguish connective tissue from smooth muscle fibres a Van Gieson elastic stain and Masson trichrome stain were performed. Smooth muscle fibres were visualized immunohistochemically with monoclonal antibody to smooth muscle α-actin (Bio Genex Laboratories, San Ramos, California, USA).

Anal endosonography

Anal endosonography (B & K Medical, Aarhus, Denmark) using a 7-MHz rotating probe, was carried out between 2 and 9 weeks before operation, and during the outpatient visit at 6 weeks after operation. The standard location for measuring internal anal sphincter (IAS) width was within the superficial external anal sphincter ring. The width of the IAS was measured with callipers in the left, right and posterior quadrants. Any IAS defect or attenuation was noted.

Statistical analysis

Paired *t* test for paired samples was used to analyse preoperative and postoperative endosonographic data.

Results

Complications and wound healing

Fourteen patients had day surgery and three patients were admitted (mean 3 days). No direct postoperative complications were seen. There were no episodes of urinary retention. During follow-up no bleeding that required medical attention or wound infection occurred. At 6 weeks 16 of 17 wounds had healed. In one woman, who had an anterior fissure, the surgical wound took 10 weeks to heal. After healing scars had the same appearance as those after open diathermy haemorrhoidectomy. No keyhole defects were present in the anal canal. Patients used the IDN cream until they were sure that their wounds had healed. A stool bulking agent was used for 2–3 weeks.

Clinical follow-up

One woman underwent rubber-band ligation for anterior mucosal prolapse 8 months after surgery. One man developed contact perianal dermatitis some 12 months after surgery which responded to hydrocortisone ointment. One woman developed a perianal abscess and fistula, having been symptom free for 22 months after fissurectomy. Anal endosonography showed the typical appearance of a fistula originating from an intersphincteric cryptoglandular abscess.

At a median follow-up of 29 (range 23–36) months there have been no recurrences. No patient noted a deterioration in continence; no incontinence to solid or liquid faeces, or soiling was noted.

Histology

In 14 patients complete excision of the fissure was performed. In three patients no base of the fissure could be jointly excised. Haemorrhoidal tissue adjacent to each side of the fissure was seen in all specimens. A defect in the anal mucosa was present in 14 patients. No inflammation was seen in 11 patients, minor inflammation was seen in three patients and moderate inflammation in another three patients. The anal mucosa was undermined adjacent to the defect in 11 patients and a fibroepithelial polyp was present in six patients. Compact connective tissue was present in the bottom of the fissure but was not apparent in the smooth muscle bundles present in the base of the fissure in 14 patients. The histological data were thought to be consistent with aspecific anodermal scar tissue, with or without an epidermal defect, in 16 patients. A typical example of the histology is shown in *Fig. 1*.

Anal endosonography

In one patient evidence of a previously performed internal sphincterotomy was present. In two further patients attenuation of the posterior IAS was seen in its most distal part only. This was not accompanied by either anterior bulging of the IAS or thickening of the IAS in the lateral quadrants. No further defects were seen in either external or internal sphincters. No endosonographic signs of fibrosis of the IAS were seen. The thickness of the IAS was not changed significantly by fissurectomy in either posterior or lateral quadrants (*Table 1*).

Discussion

This study has shown that fissurectomy in combination with IDN cream is a safe sphincter-saving alternative in the treatment of chronic fissure *in ano* not responding to conservative treatment. It is also a long-term solution.

Recent studies have shown that lateral internal sphincterotomy is detrimental to the continence mechanism[3]. The length of the sphincterotomy, and whether an open or closed technique is used are related to the incidence of incontinence[2]. Given that the surgical estimate of the length of the sphincterotomy is not always correct[4] and endosonographic evidence of sphincterotomy is sometimes absent[5], lateral internal sphincterotomy is not as standardized a procedure as might otherwise be thought.

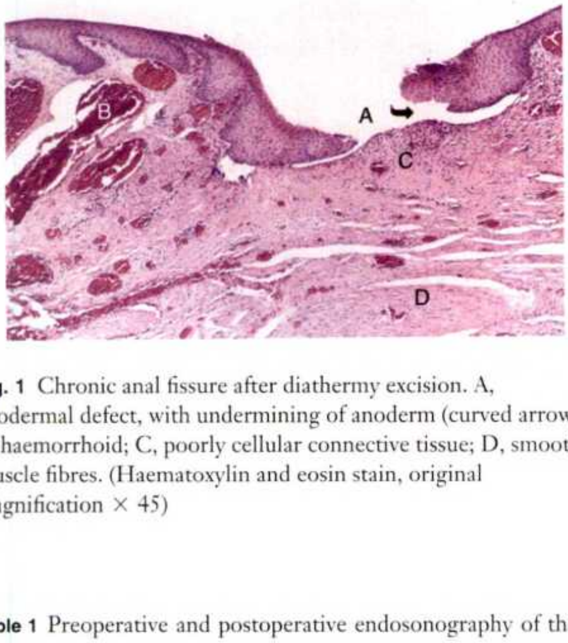

Fig. 1 Chronic anal fissure after diathermy excision. A, anodermal defect, with undermining of anoderm (curved arrow); B, haemorrhoid; C, poorly cellular connective tissue; D, smooth muscle fibres. (Haematoxylin and eosin stain, original magnification × 45)

To examine other more sparing surgical techniques it is important to look at the aetiology of chronic fissure *in ano*[6]. Both hypovascularization and hypoperfusion occur in the posterior anal commissure in approximately 85 per cent of normal people[7,8]. However, in combination with IAS hypertonia the pressure index may drop to below 0·3, which is the level at which critical ischaemia occurs[9]. This explains the poor wound healing and pain associated with chronic anal fissure. It does not explain why anterior chronic fissure *in ano* occurs in at least 10 per cent of female patients, and why pain if ischaemic in nature occurs only for a certain period after defaecation. Also the actual causative or initiating mechanism is unknown, and the mechanism of the transition from acute to chronic fissure remains obscure.

In patients with pre-existing IAS hypertonia poor wound healing may arise because of relative ischaemia. Repetitive trauma, for example large diameter of faecal bolus, may cause defects in the anal lining that heal poorly, leading to unstable scar tissue and a defect termed chronic anal fissure.

Submucosal gland infection or another inflammatory process was thought unlikely to be a primary cause of chronic anal fissure because mild to moderate, and in no instance severe, inflammation was seen in only a minority of the patients. Also no gland remnants were seen. Histological findings were consistent with anodermal scar tissue in 16 specimens and a defect was present in almost all of these. The defects lacked ulcer characteristics in that there was no debris, minimal inflammation and no hypergranulation. These findings support the central hypothesis in this study that chronic fissure *in ano* is unstable scar tissue with a central defect in a haemodynamically unfavourable location. Haemorrhoidal tissue was invariably present in all specimens. Whether or not haemorrhoidal thrombosis may contribute to the development of chronic fissure *in ano* has not been proven. However, circumstantial evidence warrants further investigation of its role in the origin of chronic anal fissure.

In one study, fibrosis of the IAS thought to be caused by myositis was linked to chronic anal fissure[10]. This was not confirmed either histologically or endosonographically in

Table 1 Preoperative and postoperative endosonography of the internal anal sphincter

	IAS width (mm)*		95 per cent c.i. of difference	P†
	Preoperative	Postoperative		
Left lateral quadrant	1·2(0·2)	1·2(0·3)	− 0·26, 0·12	0·43
Right lateral quadrant	1·2(0·2)	1·2(0·3)	− 0·36, 0·22	0·60
Posterior quadrant	1·1(0·3)	1·1(0·2)	− 0·05, 0·11	0·39

*Values are mean(s.d). IAS, internal anal sphincter; c.i., confidence interval. †Paired *t* test the present study. The fibrosis that was seen, which was in no instance excessive, was interpreted as a secondary feature of chronically disturbed wound healing, leading to a layer of poorly cellular connective tissue. No signs of myositis or smooth muscle atrophy were present.

The clinical response rate of chronic fissure *in ano* to nitric oxide donors varies widely and early enthusiasm[11–15] has diminished because of less favourable results from more recent randomized trials[16–18]. Recurrences occur frequently[18], and side-effects of nitric oxide donor cream may be experienced by up to 80 per cent of patients[17,19]. A recent study has shown that there may be a primary cholinergic dominance in patients refractory to nitric oxide treatment[20]. Not every patient with chronic fissure *in ano* may therefore respond equally to nitric oxide donors. This has recently led to alternative pathways to achieve temporary chemical sphincterotomy. Calcium re-entry blockers[21] and botulinum toxin[22,23] seem particularly promising.

In the present study little smooth muscle tissue was present in the base of the fissure where an attempt was made to excise the fissure completely. Although some smooth muscle bundles were present this did not alter the IAS width on endosonography. In this respect the present technique differs from the method described as dorsal fissurectomy and midline superficial internal sphincterotomy[24,25]. One of the possible complications of the latter technique is a keyhole defect that may lead to faecal soiling. Soiling, in this situation, is not related to changes in resting pressure[26]. In the present study no keyhole defects were seen and wounds healed in the manner of wounds following open haemorrhoidectomy. Nitric oxide donors improve anodermal blood flow[11]. It is conceivable that they may also improve postoperative wound perfusion leading to better wound healing[27]. When fissurectomy is not combined with a midline sphincterotomy, wound dehiscence and keyhole deformities, such as those that occur after anal fistulotomy, do not occur.

Diathermy fissurectomy, without sphincterotomy, is a straightforward day-care procedure with minimal short- or long-term complications. The present results need confirmation in larger randomized clinical trials.

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Short note

Optimum number of core biopsies for accurate assessment of histological grade in breast cancer

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Introduction

Establishing a histological diagnosis of breast cancer using a core-cut biopsy needle is well established with a sensitivity quoted from 67 to 98 per cent[1]. Accurate preoperative tissue diagnosis is essential before definitive surgical treatment for breast cancer.

Increasingly, patients with breast cancer are receiving neoadjuvant chemotherapy either to render tumours operable, or to shrink the tumour so that conservative surgery becomes possible[2]. Prognosis of these patients is based on the Nottingham Prognostic Index, of which tumour grade is a major component. Preoperative chemotherapy may induce considerable morphological changes so histological grading is possible only before treatment.

Accurate grading on preoperative core biopsies is necessary to establish the true grade of the tumour in patients given neoadjuvant chemotherapy. This study was carried out to ascertain the optimum number of core biopsies needed both to obtain a histological diagnosis and to grade the tumour accurately.

Patients and methods

This study was undertaken on 20 mastectomy specimens from patients undergoing breast cancer surgery following the authors' normal diagnostic and treatment protocols. The mastectomy specimen was taken fresh to the pathology department where it was oriented as it would be *in vivo*, and core biopsies were taken as they would have been in the clinic.

A small skin incision was made in the specimen with a 15-blade scalpel, the tumour was fixed with the left hand, and ten consecutive core biopsies were taken percutaneously and labelled sequentially. Biopsies were taken using a Bard Magnum® spring-loaded biopsy instrument (C. R. Bard, Covington, Georgia, USA). Bard Magnum® biopsy needles were used in conjunction with this instrument. These were 14-G 10-cm long core-cut biopsy needles, with a 19-mm biopsy notch that gave a core of standard volume.

Following fixation in 10 per cent buffered formalin, paraffin sections were cut at 4–5 μm and stained with haematoxylin and eosin. Three sections were examined from each tissue core. Slides were then labelled with a random number, to blind the observers to the origin of each tissue section. Slides were analysed by two investigators over a conference microscope, one of whom is a dedicated breast pathologist. Biopsies were graded according to the method of Bloom and Richardson, with each grade recorded as tubule formation, nuclear pleomorphism and number of mitoses. These values were then correlated with the pathology results obtained from the resection specimens; the latter were all graded by one pathologist (E.A.M.).

Results

Tumours ranged in size from 12 to 120 (mean 34) mm. Overall, 15 (8 per cent) of 200 cores were considered inadequate, showing no discernible histological features after fixation.

For a single core, the percentage of diagnostic biopsies was 74 (approximate 95 per cent confidence interval (c.i.) 65 to 83) per cent. This figure rose to 95 (95 per cent c.i. 92 to 97) per cent for the second and subsequent biopsies. As the size of the tumour increased, the figure for overall accuracy also rose ($P = 0.021$, Pearson's test).

In predicting the grade of the tumour, a single core was only 32 (95 per cent c.i. 22 to 42) per cent accurate, although this figure rose to 74 (95 per cent c.i. 65 to 83) per cent for four core biopsies. For seven sequential cores, the accuracy reached 79 (95 per cent c.i. 71 to 87) per cent and finally rose to 84 (95 per cent c.i. 78 to 90) per cent for the ninth and

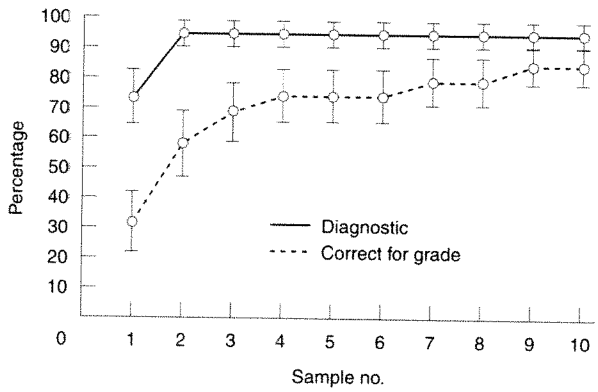

Fig. 1 Percentage of core biopsies that are diagnostic and accurate for grade according to sample number from mastectomy specimens. Error bars represent 95 per cent confidence intervals

tenth biopsies. The differences between one and four biopsies were statistically significant ($P = 0.001$, Mann–Whitney *U* test) (*Fig. 1*).

Discussion

Core needle biopsy is a convenient outpatient procedure for establishing a histological diagnosis of breast cancer which is well tolerated and acceptable to patient, surgeon and pathologist[3].

Sensitivity rates of between 74 and 89 per cent have been reported, and specificity has been reported at 100 per cent[4]. These are quoted from a number of studies with differing designs, and most fail to enumerate the number of biopsy needle passes. One previous publication quoted a diagnostic accuracy rate for a single needle pass as 67 per cent on tumours over 2 cm in diameter, and 36 per cent for tumours under 2 cm[5].

In the present study, the accuracy of histological diagnosis improved with an increasing number of biopsy needle passes and increasing tumour size This study achieved a diagnostic rate of 74 per cent for a single core-cut needle pass, rising to approximately 95 per cent for two cores. Two cores would therefore seem an optimal number for the diagnostic purpose of identifying invasive or *in situ* disease.

Concerning grade of the tumour, a single needle pass reflected the true grade of the tumour in only 32 per cent of cases. This rose to 68 per cent for three passes and to 74 per cent for four passes, at which point the results began to plateau. For ninth and tenth biopsies the accuracy rate was 84 per cent.

This lower diagnostic accuracy with respect to the grade of the tumour was mainly due to an underestimation of the mitotic count, which reached peak diagnostic accuracy of around 80 per cent after four biopsy passes. On this basis, if core biopsies are being used to grade a tumour, then the optimum number of needle passes required is four.

It is now recommended that at least four core biopsies are taken in the breast clinic.

Acknowledgements

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Original article

Detection of micrometastases in lymph nodes from patients with breast cancer

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Background: Sentinel node biopsy affords the opportunity of focused examination of lymph nodes, including the use of the reverse transcriptase–polymerase chain reaction (RT-PCR). The mammaglobin gene is expressed by breast cancers but has not been detected in histologically normal lymph nodes. This study compared mammaglobin RT-PCR with routine histology in the sentinel and non-sentinel nodes of patients with breast cancer.

Methods: Patients with breast cancer underwent tumour excision, sentinel node biopsy and axillary dissection. All nodes were bisected and half of each node was sent for routine histological examination. The other half underwent RNA extraction and mammaglobin RT-PCR.

Results: Sentinel node biopsy was successful in 50 (96 per cent) of 52 patients. Mammaglobin expression was detected in nine (8 per cent) of 119 histologically negative sentinel nodes (Clopper–Pearson 95 per cent confidence interval (c.i.) 4 to 14 per cent) and in 13 (5 per cent) of 247 histologically negative non-sentinel nodes (95 per cent c.i. 3 to 9 per cent). Mammaglobin expression was detected in four (13 per cent) of 31 patients with histologically negative sentinel nodes (95 per cent c.i. 4 to 30 per cent) and in six (14 per cent) of 44 patients with histologically negative non-sentinel nodes (95 per cent c.i. 5 to 27 per cent). The false-negative rate for sentinel node biopsy was zero using histology results and 10 per cent using RT-PCR.

Conclusion: RT-PCR screening of axillary nodes for mammaglobin expression increased the detection of breast cancer metastases compared with routine histology.

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Introduction

Staging of breast cancer involves histological examination of the ipsilateral axillary lymph nodes. However, the recurrence rate in node-negative patients is approximately 30 per cent[1]. In a proportion of these cases, metastases within the nodes may have been missed owing to observer or sampling error. Serial sectioning of axillary nodes[2,3], immunohistochemistry[4,5] and molecular biological analysis[6,7] all increase the detection of axillary metastases compared with routine histology. The technique of sentinel node biopsy may allow these techniques to become manageable at the clinical level of practice.

Serial sectioning and routine haematoxylin and eosin staining increases the detection of axillary metastases by an average of 9 per cent[8] but costs are significantly increased[9]. Immunohistochemistry using cytokeratin antibodies increases the detection of metastases by an average of 20 per cent[8] but the costs are again considerable[9].

Min *et al.*[10] evaluated seven potential breast cancer tumour markers for expression in human breast adenocarcinoma cell lines and in normal lymph nodes from patients without cancer. Of these seven markers, only mammaglobin was expressed in all cell lines and not expressed in normal lymph nodes. Mammaglobin was isolated initially from a human primary breast adenocarcinoma[11]. Its expression appears to be limited to the adult mammary gland and some tumours of the uterus[11]; it has not been detected in normal lymph nodes[11,12].

The present study examined mammaglobin expression in histologically negative sentinel and non-sentinel nodes by reverse transcriptase–polymerase chain reaction (RT-PCR).

Patients and methods

Patients and tissue

All patients gave written informed consent. Lymph node specimens were obtained from patients undergoing tumour excision and axillary dissection for cytologically or histologically proven carcinoma of the breast. Sentinel nodes were identified by a combination of the blue dye[13] and isotope[14] techniques according to the protocols of the Axillary Lymph Mapping and Nodal Axillary Clearance study. Non-sentinel lymph nodes were dissected free from the axillary fat and all nodes were bisected with a scalpel.

One half of each node was formalin fixed, paraffin embedded for histological examination and divided into 0·5-cm blocks, from each of which two sections were taken. Sections were stained with haematoxylin and eosin and examined at high power. The other half of each node was kept in RNAlater® (Ambion, Austin, Texas, USA) before storage at – 70°C. Nodes too small to be bisected were sent solely for histological examination. Five nodes from five patients without breast cancer were used as negative controls.

RNA isolation

Batches of frozen half-nodes were defrosted and each was cut into samples of between 30 and 100 mg. Each sample was homogenized in a sterile hand-held homogenizer and RNA was isolated by guanidinium thiocyanate extraction using an RNA isolation kit with spin filters (RNaqueous; Ambion), giving a final volume of 120 µl. DNA was removed by lithium chloride precipitation before the RNA was stored at – 70°C.

Reverse transcription

This was carried out using 5–20 µl RNA solution in a total reaction volume of 45 µl. The reaction mix contained RNA, 1 × first-strand buffer (Tris hydrochloride 50 mmol/l pH 8·3, potassium chloride 75 mmol/l, magnesium chloride 3 mmol/l), dithiothreitol 10 mmol/l, Superscript II® reverse transcriptase (Gibco BRL, Paisley, UK) 250 units, deoxyribonucleoside 5′-triphosphates (dNTPs) 0·4 mmol/l and random hexamers (Pharmacia, Milton Keynes, UK) 2 µg. Reaction conditions were 90°C for 3 min, 37°C for 1 h and 95°C for 3 min.

Glyceraldehyde-3-phosphate dehydrogenase polymerase chain reaction

A control amplification of a region of the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene was carried out, using the primers Gap1L (5′ TCC CAT CAC CAT CTT CCA GGA GCG 3′) and Gap2L (5′ TTG TCA TGG ATG ACC TTG GCC AGG 3′). Some 2·5 µl complementary DNA (cDNA) solution was used in a total reaction volume of 25 µl. The reaction mix contained 1 × first-strand buffer, magnesium chloride 2 mmol/l, Taq polymerase (Promega UK, Southampton, UK) 1·25 units, 2′-deoxyuridine 5′-triphosphate (dUTP) dNTP set 1·5 mmol/l, primer 0·2 nmol/l of each (PE Applied Biosystems, Warrington, UK) and uracil DNA glycosylase 0·25 units. The cycle used was 34°C for 10 min, 94°C for 10 min, then 94°C for 1 min, 60°C for 1 min and 72°C for 1 min for 40 cycles, and finally 72°C for 10 min.

Mammaglobin polymerase chain reaction

All samples expressing GAPDH underwent mammaglobin PCR using the primers D2 (5′ ATA AGA AAG AGA AGG TGT GG 3′) and D2102 (5′ CAG CGG CTT CCT TGA TCC TTG 3′). Some 2·5 µl cDNA solution was used in a total reaction volume of 25 µl. The reaction mix contained 1 × first-strand buffer, magnesium chloride 2 mmol/l, Taq polymerase 1·25 units, dUTP dNTP set 1·5 mmol/l, primer 0·02 nmol/l of each and uracil DNA glycosylase 0·25 units. The cycle used was 94°C for 10 min, then 94°C for 1 min, 60°C for 1 min, 72°C for 1 min for 40 cycles, and finally 72°C for 10 min.

Gel electrophoresis

RNA samples from every node taken were reverse transcribed and amplified in duplicate on separate plates. Occasional discrepancies were resolved by repeating both the RT and PCR steps. PCR products were run on 2 per cent agarose gels stained with ethidium bromide and visualized under ultraviolet light.

Statistical analysis

As the two data sets were paired, McNemar's test and Clopper–Pearson confidence intervals (c.i.) were used for analysis.

Results

Fifty-two patients with a mean age of 59 (range 28–84) years were recruited into the study. There were 50 women and two men. All patients underwent sentinel node biopsy, tumour excision and completion level I axillary clearance. Sentinel nodes were identified in 50 (96 per cent) of the 52 patients. In total, 159 sentinel nodes (mean 3 per patient, range 1–9) and 406 non-sentinel nodes were excised from the 50 patients for whom sentinel node biopsy was successful. Seven sentinel and 103 non-sentinel nodes were too small to be bisected, and in four sentinel and 35 non-sentinel nodes the RNA extraction step was unsuccessful. Therefore, 148 sentinel and 268 non-sentinel nodes were examined by both techniques.

Sentinel nodes

Looking at individual nodes, nine histologically negative sentinel nodes expressed mammaglobin and five histologically positive sentinel nodes did not express mammaglobin. Looking at each patient, there were four patients with histologically positive nodes that did not express mammaglobin and four with histologically negative nodes in which mammaglobin expression was detected.

Non-sentinel nodes

Looking at individual nodes, 13 histologically negative non-sentinel nodes expressed mammaglobin and two histologically positive non-sentinel nodes did not express mammaglobin. Using McNemar's test the difference in favour of mammaglobin PCR was statistically significant ($P < 0{\cdot}01$). Looking at each patient, there was one patient with histologically positive nodes that did not express mammaglobin and six with histologically negative nodes in which mammaglobin expression was detected. This difference in favour of mammaglobin PCR did not quite achieve statistical significance ($P = 0{\cdot}06$).

Histologically negative nodes

Mammaglobin expression was detected in nine (8 per cent) of 119 histologically negative sentinel nodes (Clopper–Pearson 95 per cent c.i. 4 to 14 per cent) and 13 (5 per cent) of 247 histologically negative non-sentinel nodes (95 per cent c.i. 3 to 9 per cent). Mammaglobin expression was detected in four (13 per cent) of 31 patients with histologically negative sentinel nodes (95 per cent c.i. 4 to 30 per cent) and six (14 per cent) of 44 patients with histologically negative non-sentinel nodes (95 per cent c.i. 5 to 27 per cent).

False-negative rate

The false-negative rate using histology results was zero. Twenty-one patients had one or more lymph nodes that expressed mammaglobin. In two of these patients the sentinel nodes did not express mammaglobin, giving a false-negative rate of 10 per cent for sentinel node biopsy using RT-PCR criteria alone.

Discussion

RT-PCR is an ultrasensitive technique that may allow detection of occult metastases in patients with breast cancer. However, the specificity of marker messenger RNA (mRNA) detection must be particularly high when using RT-PCR because a false positive results if occasional normal cells express the marker. None of the five control nodes in this study expressed mammaglobin. On the basis of this and other published data[12,15–17], mammaglobin appears to be both a specific and sensitive marker for breast cancer.

Earlier studies demonstrated mammaglobin expression in histologically positive axillary lymph nodes from patients with breast cancer[12,15]. Recent studies have demonstrated mammaglobin expression in some histologically negative nodes, including sentinel nodes[16,17], although only the blue dye technique was used to identify sentinel nodes. The present study demonstrated mammaglobin expression in significant numbers of histologically negative sentinel and non-sentinel lymph nodes: of 31 patients (of 50 total) with histologically negative nodes, six expressed mammaglobin. This may explain a significant proportion of the node-negative patients who develop recurrent breast cancer.

The prognosis for patients with micrometastases detected by either serial sectioning and routine staining[18,19] or immunohistochemistry[2,4,20] remains uncertain, although a study by Rosen *et al.*[21] indicated no survival disadvantage at 6 years, but some disadvantage at 10 years. The prognostic significance of micrometastases detected by RT-PCR remains untested.

Comparing the results for sentinel and non-sentinel nodes establishes the false-negative rate of sentinel node biopsy when PCR criteria are used to detect micrometastases: two of 21 patients.

There are three possible explanations for the situation of histologically positive nodes in which mammaglobin expression was not detected:

1. A true false-negative situation in which RT-PCR was unable to detect mammaglobin mRNA despite it being present.
2. Sampling error; the portion of the node containing a metastatic focus may be sent solely for one test.
3. Mammaglobin expression levels; although mammaglobin is overexpressed in 23 per cent of primary breast cancers[11], recent work suggests that up to 20 per cent of tumours do not express mammaglobin at all[12,15].

Further studies are necessary to assess the role of mammaglobin mRNA detection in determining the prognosis in patients with breast cancer. Patients with histologically positive lymph nodes need not be further assessed. Assessment of primary tumours could be undertaken to find node-negative patients who do not express mammaglobin in the tumour. Staging of patients with mammaglobin-positive tumours and negative axillary histology may then be aided by RT-PCR assessment of their axillary nodes.

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Prospective study of open preperitoneal mesh repair for recurrent inguinal hernia

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Background: Recurrent inguinal hernia presents a significant clinical problem with high re-recurrence and complication rates, particularly when an anterior approach is used. This study evaluated the open preperitoneal approach for repair of recurrent inguinal hernia.

Methods: This was a prospective cohort study of 101 consecutive patients with 114 recurrent inguinal hernias. All were operated on using an open preperitoneal technique and prosthetic mesh by the method of Stoppa or Wantz. Follow-up was at 2–6 weeks, 15 and between 42 and 54 months.

Results: There were no major complications. There was one infection and one case of retention of urine. There were no testicular complications. There were five recurrences, all within 6 months of operation, four of which were among the first 20 cases. Modifications to the original technique were made, and one recurrence occurred in the remaining 81 patients (1 per cent) or 106 hernias (1 per cent).

Conclusion: Preperitoneal mesh repair gives results far superior to those of the commonly used anterior approach. It is safer and easier to learn than laparoscopic repair and is the procedure of choice for complex multirecurrent inguinal hernia.

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Introduction

Recurrent inguinal hernia remains a significant clinical problem despite advances in surgical technique. Comprehensive audit from national hernia registers in Sweden[1] and Denmark[2] has shown an incidence of recurrence of 16–18 per cent following primary repair using a variety of techniques. Operating on recurrent hernias is technically challenging and re-recurrence rates of over 30 per cent have been reported[3,4].

Increasing use of prosthetic mesh has improved the re-recurrence rate[5,6], but the anterior approach still has the disadvantage of reoperating through scar tissue with the risk of damage to the testicular blood supply and sensory nerves[7]. Reoperating using a preperitoneal approach, either open or laparoscopic, addresses these problems.

The Stoppa operation[8] was developed to deal with complex or multirecurrent groin hernias by placing a large piece of prosthetic mesh in the preperitoneal space. Wantz[9] adapted this operation for the repair of unilateral recurrences, both techniques being dubbed 'giant prosthetic reinforcement of the visceral sac'. Two of the authors visited both Stoppa and Wantz in 1995 to become familiar with the technique.

The aim of this prospective cohort study was to follow the immediate and long-term outcome in the first 101 patients.

Patients and methods

Between March 1995 and July 1996, 114 patients had a recurrent inguinal hernia repaired. Ten patients with a failed laparoscopic repair and three patients aged over 80 years underwent repair via an anterior approach and were excluded; 101 patients (all men) were therefore entered into the study.

The mean age of the patients was 54 (range 26–85) years and mean body mass index was 25 (range 21–32) kg/m^2. Sixty-eight patients had a unilateral recurrence. Thirty-three patients had bilateral hernias of whom 13 had bilateral recurrences and 20 had a unilateral recurrent hernia with a contralateral primary hernia. Thus the total number of hernias repaired was 134, of which 114 were recurrent. Seventy-four had been repaired once previously and the remainder were multirecurrent.

Each patient emptied his bladder immediately before operation and none was catheterized. Ninety-eight patients had general anaesthesia, two had a spinal anaesthetic and one local anaesthesia. Cefuroxime 1·5 g was given intravenously with induction of anaesthesia, and the operating table was tilted 20–30° head down. The repair was as described by Stoppa and Warlaumont[8] for bilateral repairs and by Wantz[10] for unilateral repairs using a Pfannenstiel incision for the former and a transverse incision just below the level of the iliac crest for the latter. In bilateral repairs a large piece (30 × 15 cm) of Mersilene mesh (Ethicon, Edinburgh, UK) was cut to size and shape, and the central point of the lower border was anchored to the back of the pubis with one non-absorbable suture. With the unilateral procedure Mersilene mesh was shaped from a 15 × 15-cm piece and in the first 20 patients was attached superiorly as described by Wantz[10]. The technique was modified for defects larger than 5 cm in diameter by placing an additional piece of Prolene mesh (Ethicon) to cover the gap widely before inserting the 'giant' Mersilene prosthesis. In the last 60 patients the mesh was changed from Mersilene to Prolene (15 × 15 cm), attached inferiorly with non-absorbable sutures at the pubic symphysis and the superior pubic ramus just medial to the femoral vein. The upper portion of the mesh which extended above the incision was picked up with two or three bites of the 2/0 polypropylene closing suture. A vacuum drain was used routinely.

Patients were discharged the day after operation with oral analgesics and diclofenac suppositories. They were examined between 2 and 6 weeks after operation, and complications were noted. Subsequently they were contacted between 12 and 15 months after operation, and again over a 6-month interval from June to December 1999, and asked to return for examination.

Results

There were no major intraoperative difficulties or cardiopulmonary, cerebrovascular or thrombotic complications. The only serious complication encountered was one deep infection that required open drainage; this responded to antimicrobial therapy and the mesh was not removed. One patient developed retention of urine following a spinal anaesthetic and overenthusiastic intravenous fluid administration, and remained in hospital for a further 24 h. Five patients noticed a recurrent swelling within 6 months of operation and reported this before a scheduled follow-up visit. Four of these recurrences occurred in the first 20 patients.

At 12–18 months the remaining 96 patients were contacted. Three, who lived abroad, could not be traced. Fifty-three patients returned for examination and no recurrences were found. There were no cases of testicular atrophy, anterior thigh numbness or chronic groin pain. Forty patients could not attend for examination because of the distance involved. None reported any symptoms or signs of recurrence and as all patients had at least one previous failed hernia their judgement was accepted.

Four years after the date of operation all 93 patients were contacted again. One patient could not be traced. Two elderly patients had died from unrelated causes and relatives reported that the hernias had not recurred. Forty patients were unable to return for examination but confirmed in a written questionnaire that the hernia had not recurred. Twenty-five of the remaining 50 patients attended for examination and 25 patients were telephoned by a surgeon. None of these 92 patients had developed a recurrence.

Discussion

This prospective study of 101 patients demonstrates the effectiveness of open preperitoneal mesh (OPPM) repair for recurrent inguinal hernia. When the first 20 operations resulted in four recurrences the technique was modified and there was a single recurrence in the subsequent 81 patients or 106 hernias (1 per cent), all followed for a minimum of 4 years. This low incidence of recurrence, low complication rate and high level of patient satisfaction is in accord with other studies of OPPM repair[8,9,11–17].

Recurrences after mesh repair of hernias occur early and are related to technical factors such as inadequate dissection, insufficient prosthesis size and fixation, and surgeon inexperience[17,18]. In this series two recurrences were due to inadequate fixation of the inferomedial corner of the mesh, one to insufficient prosthesis size and one to the flexible Mersilene prolapsing through an extremely large multi-recurrent defect with extensive tissue loss. Prolene mesh was found easier to position than the more flexible Mersilene[19] and the method of mesh attachment was made similar to that used by Rives *et al.*[20].

The preperitoneal approach for recurrent inguinal hernia avoids reoperating through distorted anatomy and scar tissue, markedly reducing the risk of damage to the testicular vessels, and permits inspection of all potential groin hernia sites. Through an open incision the dissection is rapid and structures are easily and widely visible; its benefits have long been proclaimed[21,22]. Although access is excellent via this route the results of recurrent hernia repair remained poor until prosthetic mesh was added to the repair[23,24]. Stoppa *et al.*[8,25] placed a large sheet of mesh, via a midline incision, in the preperitoneal plane without closing the defect or fixing the mesh. Wantz[10] described a unilateral version of the procedure through a high transverse incision.

Even with complex or multirecurrent hernias the method gave impressive results.

Despite these clear benefits and excellent results, OPPM repair has not been widely adopted, in part because of unfamiliarity with this approach. In a recent survey[26] of surgical practice 85 per cent of repairs for recurrent inguinal hernia were open anterior procedures (76 per cent mesh and 9 per cent non-mesh) and only 15 per cent were preperitoneal (9 per cent laparoscopic and 6 per cent open preperitoneal).

The advent of therapeutic laparoscopic surgery provided a means of entering the preperitoneal space without an open incision. The technique was adopted with widespread enthusiasm, followed by alarming reports of vessel and viscus injury, nerve damage and high recurrence rates when inadequately sized pieces of mesh were used by inexperienced surgeons[27,28].

It was clear that there was a considerable learning curve for laparoscopic repair, estimated by some to be at least 50 repairs[29–31]. The UK Medical Research Council study[32] concluded that laparoscopic hernia repair had a lengthy learning curve and should be performed only by individuals who have considerable experience with the technique. In contrast the authors' experience with OPPM is that, although there is undoubtedly a learning curve, it is short: in this series 20 cases between three surgeons, as is the experience of others[8,10,33,34].

The EU Hernia Trial[35] found that the potential for rare but serious complications does not justify the use of laparoscopic repair for uncomplicated unilateral primary hernias although it is now being advocated for bilateral and recurrent hernias. The reported short-term recurrence rates are excellent[34–39], but do the claimed short-term benefits of reduced postoperative discomfort and faster return to normal activities justify its use in these situations?

Two randomized trials have compared laparoscopic with OPPM repair for bilateral[34] and a mixed group[29] of hernias and found no significant difference in short-term recurrence rates. Aitola *et al.*[40] compared laparoscopic repair with OPPM repair for recurrent inguinal hernia but used an open transinguinal approach, negating most of the advantages of the preperitoneal technique. Nevertheless the recurrence rate at 18 months was 13 per cent in the laparoscopic group and 8 per cent in the open group. Beets *et al.*[33] compared laparoscopic repair with OPPM for recurrent hernia; re-recurrence rates were 12 and 2 per cent respectively, and it was also confirmed that open preperitoneal repair is an easier procedure with a shorter learning curve. Furthermore the laparoscopic approach cannot be used in patients with incarcerated or large inguinoscrotal hernias[34], where there is extensive tissue loss (absent inguinal ligament) or in patients unfit for general anaesthesia.

In the present series postoperative discomfort was low, requiring only oral analgesia and permitting rapid mobility so that patients could be discharged the day after operation. Despite the minimal postoperative patient discomfort after OPPM repair noted in the majority of series there is wide variation reported in the duration of hospital stay, ranging from 1 to 6 days, although this may simply reflect varying expectations and cultural differences[8,12–17]. Three comparative studies found more postoperative discomfort and a longer recovery time with the open operation[29,33,34], although all used a lower midline incision. The present experience accords with that of Rignault[11], who concluded that a Pfannenstiel incision causes the least discomfort as well as the lowest risk of incisional hernia. In two studies[15,16] patients were routinely catheterized, a procedure that was not found to be necessary in this series. Indeed routine catheterization may precipitate urinary problems. The very low incidence of infection and the absence of testicular complications in this study accords with others[8–17].

In conclusion, the OPPM repair for recurrent inguinal hernia is highly effective in achieving a low recurrence rate. It is easier to learn and safer than laparoscopic repair, and should be the procedure of choice for all recurrent groin hernias apart from laparoscopic failures.

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Original article

Prediction of serious complications in patients admitted to a surgical ward

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Background: Prediction of complications is an essential part of risk management in surgery. Knowing which patients are at high risk of developing complications will contribute to the quality and cost reduction of surgery.

Methods: All patients admitted to a general surgical ward during a 1-year interval were followed until 30 days after discharge. Complications and data on potential risk factors were recorded prospectively. Relative risks were calculated for each risk factor and predictive values for the development of a serious or minor complication were computed using logistic regression analysis. The predictive values of different combinations of variables were expressed as receiver operating characteristic curves.

Results: Of 3075 patients, 375 suffered one or more serious complications and 319 experienced a minor complication. A model was developed for prediction of serious complications, consisting of 11 variables, with an area under the curve (AUC) of 0·79 (95 per cent confidence interval (c.i.) 0·76 to 0·81). The prognostic value of the model for minor complications (seven variables) was lower (AUC 0·68 (95 per cent c.i. 0·65 to 0·71)).

Conclusion: Serious complications in patients admitted to a surgical ward can be predicted using a model consisting of 11 variables. The risk score can be used in the decision-making process before surgery.

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Introduction

Risk management is an increasingly important healthcare issue. Doctors are now legally bound to inform patients of the potential risks involved with treatment. Essential to the decision-making process before surgery is identification of those patients most at risk of developing a serious complication.

In the past, various scoring systems, such as the American Society of Anesthesiologists (ASA) physical status classification[1], Acute Physiology and Chronic Health Evaluation (APACHE) II[2], and Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM)[3] have been used to predict both morbidity and death in surgical patients.

ASA scores are easy to derive but are subjective and subject to variability; they therefore lack reproducibility[4]. APACHE II is complex in use and consists, apart from age and chronic health variables, mainly of an acute physiology score not suited to assess risk in a 'healthy' surgical population. POSSUM proved useful for comparative audit, but for scoring each patient requires a chest radiograph, an electrocardiogram (ECG) and a blood sample[5,6].

An ideal model to predict complications in surgical patients should be simple and readily applicable to all patients whether operated or not. In daily routine few patients need a chest radiograph, ECG and/or a blood sample (other than for typing and cross-matching) for preoperative evaluation. These parameters are not therefore suited for use in a model predicting complications in a general low-risk surgical population.

When developing a predictive model for complications in surgical patients, an accurate estimate of the incidence of these complications is needed. Therefore a proper definition of a complication, with a low detection threshold, is necessary. As not all complications are of similar consequence they should be graded according to severity. The aim of this study was to identify a minimal set of relevant patient-, disease- and surgery-related variables to predict both serious and minor complications in surgical patients.

Patients and methods

All patients admitted to the surgical ward of the University Medical Centre in Utrecht, the Netherlands, during a 1-year period were included in this prospective follow-up study. Patients were followed throughout their hospital stay and for 30 days after discharge. From January 1996 to January 1997, 3075 consecutive patients were admitted or readmitted (53 per cent males and 47 per cent females). Age ranged from 13 to 95 (median 51) years. Emergency and day-care surgical admissions were also included in the study. Patients treated without operative intervention, who were admitted for diagnostic purposes or for observation, were included. On admission data were collected on the potential risk factors listed in *Table 1*. These risk factors were selected after a review of the relevant literature.

The diagnoses at admission were classified according to whether the disease or injury was 'central', i.e. involving part of the trunk, or peripheral. Operations were classified according to the year in which a surgical trainee is expected to be able to perform the operation. Class 1 consisted of operations potentially performed by a surgical trainee in the first year of training, for example drainage of an abscess, and class 2 of operations for trainees in their second year, for example appendicectomy and repair of a groin hernia. Class 7 consisted of operations beyond the competence of sixth-year surgical trainees, including partial hepatectomy and total gastrectomy. Operations of classes 4–7 were considered to represent major surgery.

A complication was defined as any state or event unfavourable to a patient's health that arose during admission or within 30 days after discharge and caused either unintentional injury or required additional treatment[7]. Complications were classified according to severity into seven grades based on the classification of Clavien *et al.*[8], in which grade 1 comprised minor temporary injury not requiring intervention and a grade 7 complication resulted in death. Any complication that required additional surgical intervention was considered grade 5. The most serious complication was used as the outcome of interest. If this most serious complication was graded 1–4, the patient was considered to have had only a minor complication. If a grade 5–7 complication had occurred, the patient was considered to have had a serious complication. Patients without complications were used as the reference group.

Patients were followed intensively throughout their hospital stay and were screened for complications by both nurses, the responsible medical team and a researcher especially assigned to the project. Patients were seen at the outpatient department at least 30 days after discharge or followed by telephone or postal questionnaire.

Statistical analysis

Baseline characteristics of patients were summarized in terms of frequencies and percentages for the categorical variables. Continuous variables, such as age and body mass index, were evaluated for normality and then categorized to improve interpretation. The choice of reference category was based on obvious criteria, for example elective admission and ASA grade I, or on numbers, with the biggest group comprising the reference category. Since multivariate analysis required all data to be present for all patients[9], imputation techniques were used (SPSS version 10; SPSS, Chicago, Illinois USA) to fill in the missing values of some variables without disturbing the relationship between the variables as observed in the data. This allowed inclusion of all patients in the analysis and reduced bias[10].

Univariate and multivariate logistic regression analyses were applied to evaluate the relationships between baseline characteristics and the occurrence of complications. Relative risks and odds ratios were calculated, comparing the risk of developing a minor or serious complication with respect to patients with an uneventful course. A full multivariate model was derived that included all the potential predictors. This model was simplified according to statistical criteria. Variables that showed no significant association with a minor or a serious complication ($P \geq 0{\cdot}15$) were excluded. To assess their influence a cumulative model was constructed starting with patient-related factors (age, weight loss, ASA physical status, history of pulmonary disease for minor complications; gender, smoking behaviour, renal failure and all above mentioned variables for serious complications). Later, factors associated with the (acute) disease of the patient (diagnosis for minor complications, and diagnosis and urgency of admission for serious complications) were added. Finally, the influence of surgery (the extent of surgery and if it was performed as a day-care procedure or not) was included in the model.

To express the predictive power of the model, area under the receiver operating characteristic (ROC) curve was calculated for four different models containing combinations of significant variables as follows: model 1, patient-related factors; model 2, patient- and disease-related factors; model 3, patient-, disease- and surgery-related factors; and model 4, all significant variables (13 in the case of serious and nine in the case of minor complications). Calibration of the model was tested with the Hosmer–Lemeshow goodness-of-fit test[11].

To be able to predict the risk for an individual patient, a risk score was developed containing the coefficients of the model with the predictive variables. The risk of a patient developing a complication is $1/(1 + e^{-Z})$ (Appendix).

Table 1 Distribution of risk factors in patients without, with minor and with serious complications

	No complication (n = 2381)	Minor complication (n = 319)	Serious complication (n = 375)
Age (years)			
< 40	852 (36)	76 (24)	67 (18)
40–69	1136 (48)	168 (53)	204 (54)
70–79	271 (11)	56 (18)	77 (21)
> 79	122 (5)	19 (6)	27 (7)
Sex			
Male	1246 (52)	166 (52)	231 (62)
Female	1135 (48)	153 (48)	144 (38)
Referral source			
Patient's initiative	179 (8)	14 (4)	11 (3)
General practitioner	655 (28)	65 (20)	75 (20)
Ambulance	214 (9)	29 (9)	37 (10)
Consultant	909 (38)	143 (45)	159 (42)
Consultant elsewhere	321 (13)	55 (17)	81 (22)
Other	81 (3)	12 (4)	9 (2)
Unknown	22 (1)	1 (0)	3 (1)
Day-care surgery			
Yes	507 (21)	38 (12)	18 (5)
No	1874 (79)	281 (88)	357 (95)
Urgency of admission			
Elective	1498 (63)	192 (60)	177 (47)
Urgent (but planned)	211 (9)	26 (8)	39 (10)
Emergency	653 (27)	98 (31)	153 (41)
Unknown	19 (1)	3 (1)	6 (2)
Route of admission			
Outpatient department	1492 (63)	195 (61)	173 (46)
Emergency department	674 (28)	82 (26)	124 (33)
Other department	64 (3)	18 (6)	34 (9)
Other hospital	86 (4)	15 (5)	32 (9)
Otherwise	38 (2)	5 (2)	6 (2)
Unknown	27 (1)	4 (1)	6 (2)
Diagnosis			
Central part of body	1153 (48)	192 (60)	248 (66)
Limbs	1228 (52)	127 (40)	127 (34)
Body mass index (kg/m^2)			
< 27·3	1741 (73)	214 (67)	249 (66)
≥ 27·3	448 (19)	71 (22)	82 (22)
Unknown	192 (8)	34 (11)	44 (12)
Weight loss (kg per 3 months)			
≥ 10	72 (3)	20 (6)	27 (7)
< 10	2282 (96)	293 (92)	340 (91)
Unknown	27 (1)	6 (2)	8 (2)
ASA grade			
I	1789 (75)	199 (62)	198 (53)
II	380 (16)	68 (21)	85 (23)
III	133 (6)	39 (12)	57 (15)
IV	29 (1)	6 (2)	14 (4)
V	6 (0)	3 (1)	10 (3)
Unknown	44 (2)	4 (1)	11 (3)
Smoking*			
Yes	734 (31)	93 (29)	129 (34)
No	1510 (63)	202 (63)	198 (53)
Unknown	137 (6)	24 (8)	48 (13)
Cardiac disease†			
Yes	264 (11)	47 (15)	74 (20)
No	2056 (86)	267 (84)	285 (76)
Unknown	61 (3)	5 (2)	16 (4)
Hypertension‡			
Yes	405 (17)	79 (25)	88 (23)
No	1929 (81)	236 (74)	277 (74)
Unknown	47 (2)	4 (1)	10 (3)
Pulmonary disease§			
Yes	170 (7)	45 (14)	70 (19)
No	2170 (91)	271 (85)	295 (79)
Unknown	41 (2)	3 (1)	10 (3)
Diabetes¶			
Yes	110 (5)	26 (8)	26 (7)
No	2250 (94)	293 (92)	344 (92)
Unknown	21 (1)	0 (0)	5 (1)
Renal failure**			
Yes	85 (4)	12 (4)	37 (10)
No	2245 (94)	301 (94)	333 (89)
Unknown	51 (2)	6 (2)	5 (1)
Immunological disorder††			
Yes	60 (3)	10 (3)	18 (5)
No	2302 (97)	309 (97)	353 (94)
Unknown	19 (1)	0 (0)	4 (1)
Self-supporting			
Yes	2297 (96)	299 (94)	350 (93)
No	65 (3)	20 (6)	21 (6)
Unknown	19 (1)	0 (0)	4 (1)
Surgery			
No	384 (16)	19 (6)	12 (3)
Minor	872 (37)	99 (31)	74 (20)
Major	1111 (47)	196 (61)	288 (77)
Unknown	14 (1)	5 (2)	1 (0)

Values in parentheses are percentages. *Currently smoking or stopped smoking < 1 year ago; †asymptomatic but after myocardial infarction/with arrhythmia on electrocardiogram or symptomatic owing to angina pectoris or cardiac failure; ‡resting diastolic pressure ≥ 90 mmHg; §any form of dyspnoea or an abnormal chest radiograph; ¶necessitating medication; **serum creatinine ≥ 130 µmol/l, on dialysis or with renal transplant; ††due to disease or medication. ASA, American Society of Anesthesiologists

Results

Of the 3075 included patients, 2381 had an uneventful course, 319 patients developed minor (grade 1–4), and 375 one or more serious complications (grade 5–7). Ninety-seven patients died in hospital, 116 were discharged to another ward or hospital and were not followed, and 197 were readmitted during follow-up. Of the remaining patients, 1253 were seen at the outpatient department, 1101 were contacted by phone and 145 returned postal questionnaires. Follow-up data are missing in 166 patients.

Table 1 shows the distribution of risk factors in patients with and without complications. *Table 2* shows the univariate relative risk of developing a minor or serious

Table 2 Results of univariate analysis: relative risks of a serious or minor complication for all variables

	Relative risk for Serious complication	Relative risk for Minor complication
Age (years)		
< 40	1·0	1·0
40–69	2·1 (1·6, 2·7)	1·6 (1·2, 2·0)
70–79	3·0 (2·2, 4·1)	2·1 (1·5, 2·9)
> 79	2·5 (1·6, 3·8)	1·6 (1·0, 2·6)
Sex		
Female	1·0	1·0
Male	1·4 (1·1, 1·7)	1·0 (0·8, 1·2)
Referral source		
Patient's initiative	0·4 (0·2, 0·7)	0·5 (0·3, 0·9)
General practitioner	0·7 (0·5, 0·9)	0·7 (0·5, 0·9)
Ambulance	1·0 (0·7, 1·4)	0·9 (0·6, 1·3)
Consultant	1·0	1·0
Consultant elsewhere	1·4 (1·1, 1·7)	1·1 (0·8, 1·4)
Other	0·7 (0·4, 1·3)	0·9 (0·5, 1·6)
Day-care surgery		
No	1·0	1·0
Yes	0·2 (0·1, 0·3)	0·5 (0·4, 0·7)
Urgency of admission		
Elective	1·0	1·0
Urgent (but planned)	1·5 (1·1, 2·0)	1·0 (0·7, 1·4)
Emergency	1·8 (1·5, 2·2)	1·1 (0·9, 1·4)
Route of admission		
Outpatient department	1·0	1·0
Emergency department	1·5 (1·2, 1·9)	0·9 (0·7, 1·2)
Other department	3·3 (2·5, 4·5)	1·9 (1·2, 2·9)
Other hospital	2·6 (1·9, 3·6)	1·3 (0·8, 2·1)
Otherwise	1·3 (0·6, 2·8)	1·0 (0·4, 2·3)
Diagnosis		
Limbs	1·0	1·0
Central part of body	1·9 (1·5, 2·3)	1·5 (1·2, 1·9)
Body mass index (kg/m^2)		
< 27·3	1·0	1·0
≥ 27·3	1·2 (1·0, 1·6)	1·3 (1·0, 1·6)
Weight loss (kg per 3 months)		
< 10	1·0	1·0
≥ 10	2·1 (1·5, 2·9)	1·9 (1·3, 2·9)
ASA grade		
I	1·0	1·0
II	1·8 (1·5, 2·3)	1·5 (1·2, 2·0)
III	3·0 (2·3, 3·9)	2·3 (1·7, 3·1)
IV	3·3 (2·1, 5·1)	1·7 (0·8, 3·6)
V	6·3 (4·2, 9·4)	3·3 (1·3, 8·5)
Smoking*		
No	1·0	1·0
Yes	1·3 (1·0, 1·6)	1·0 (0·8, 1·2)
Cardiac disease†		
No	1·0	1·0
Yes	1·8 (1·4, 2·3)	1·3 (1·0, 1·8)
Hypertension‡		
No	1·0	1·0
Yes	1·4 (1·1, 1·8)	1·5 (1·2, 1·9)
Pulmonary disease§		
No	1·0	1·0
Yes	2·4 (1·9, 3·1)	1·9 (1·4, 2·5)
Diabetes¶		
No	1·0	1·0
Yes	1·4 (1·0, 2·0)	1·7 (1·2, 2·4)
Renal failure**		
No	1·0	1·0
Yes	2·3 (1·8, 3·1)	1·1 (0·6, 1·8)
Immunological disorder††		
No	1·0	1·0
Yes	1·7 (1·1, 2·6)	1·2 (0·7, 2·2)
Self-supporting		
Yes	1·0	1·0
No	1·8 (1·3, 2·7)	2·0 (1·4, 3·0)
Surgery		
No	0·4 (0·2, 0·7)	0·5 (0·3, 0·7)
Minor	1·0	1·0
Major	2·6 (2·1, 3·6)	1·5 (1·2, 1·8)

Values in parentheses are 95 per cent confidence intervals. *Currently smoking or stopped smoking < 1 year ago; †asymptomatic but after myocardial infarction/with arrhythmia on electrocardiogram or symptomatic owing to angina pectoris or cardiac failure; ‡resting diastolic pressure ≥ 90 mmHg; §any form of dyspnoea or an abnormal chest radiograph; ¶necessitating medication; **serum creatinine ≥ 130 μmol/l, on dialysis or with renal transplant; ††due to disease or medication. ASA, American Society of Anesthesiologists

complication for all variables in relation to an uneventful hospital stay. *Table 3* shows the odds ratios resulting from a logistic regression analysis of the four different models containing prognostic variables associated with a serious complication. *Table 4* shows the odds ratios of the four different models with the nine variables associated with a minor complication.

The predictive power of the various models for developing a serious complication is expressed by the area under the ROC curve in *Fig. 1*. Model 1, with only patient-related factors, had an area under curve of 0·69 (95 per cent confidence interval (c.i.) 0·67 to 0·72). When disease- and surgery-related factors were added to the model, the areas under the curves became 0·72 (95 per cent c.i. 0·69 to 0·75) (model 2) and 0·79 (95 per cent c.i. 0·76 to 0·81) (model 3) respectively. Model 4, with all 13 significant risk factors for a serious complication, had an area under the curve of 0·80 (95 per cent c.i. 0·77 to 0·82).

Model 3 was used to develop the final risk score. Although significantly associated with the development of a serious complication, two variables in this model, namely referral source and route of admission, were left out as their contribution to the predictive power was minimal in exchange for obscuring the risk score. The model was well calibrated which means that the predicted probabilities matched the observed complication rates (P = 0·80, Hosmer–Lemeshow goodness-of-fit test)[11]. The 11 variables used in the risk score were age, sex, weight loss, ASA

Table 3 Multivariate analysis of area under receiver operating characteristic curve and odds ratios of variables significantly associated with a serious complication in four different models

	Model 1 (*n* = 2756)	Model 2 (*n* = 2731)	Model 3 (*n* = 2716)	Model 4 (*n* = 2675)
Missing data	0	25	40	81
AUC	0·69 (0·67, 0·72)	0·72 (0·69, 0·75)	0·79 (0·76, 0·81)	0·80 (0·77, 0·82)
Odds ratios				
Patient-related factors				
Age (years)				
< 40	1·0	1·0	1·0	1·0
40–69	1·9 (1·4, 2·6)	2·0 (1·5, 2·7)	1·7 (1·3, 2·4)	1·8 (1·3, 2·5)
70–79	2·5 (1·7, 3·6)	2·7 (1·8, 3·9)	2·2 (1·5, 3·3)	2·3 (1·5, 3·5)
> 79	2·2 (1·3, 3·7)	1·9 (1·1, 3·3)	1·5 (0·9, 2·7)	1·6 (0·9, 2·8)
Male sex	1·4 (1·1, 1·8)	1·3 (1·0, 1·7)	1·4 (1·1, 1·8)	1·4 (1·1, 1·8)
Major weight loss	2·1 (1·3, 3·3)	1·9 (1·1, 3·1)	1·8 (1·1, 3·1)	1·8 (1·1, 3·1)
ASA grade				
I	1·0	1·0	1·0	1·0
II	1·4 (1·0, 1·9)	1·4 (1·0, 1·9)	1·3 (1·0, 1·8)	1·3 (0·9, 1·8)
III	2·4 (1·6, 3·5)	2·2 (1·5, 3·3)	2·1 (1·4, 3·1)	2·1 (1·4, 3·2)
IV	2·8 (1·4, 5·7)	2·4 (1·2, 4·8)	2·1 (1·0, 4·5)	1·9 (0·9, 4·1)
V	9·2 (3·2, 26·4)	5·9 (2·0, 17·6)	3·6 (1·2, 11·2)	3·2 (1·0, 9·9)
Smoking*	1·3 (1·0, 1·7)	1·4 (1·1, 1·8)	1·3 (1·0, 1·7)	1·4 (1·1, 1·8)
Pulmonary disease†	1·8 (1·3, 2·5)	1·8 (1·3, 2·5)	1·9 (1·3, 2·7)	1·9 (1·3, 2·7)
Renal failure‡	1·5 (1·0, 2·4)	1·6 (1·0, 2·6)	1·4 (0·9, 2·3)	1·3 (0·8, 2·2)
Disease-related factors				
Central diagnosis	–	1·8 (1·4, 2·3)	2·0 (1·5, 2·5)	1·9 (1·5, 2·5)
Admission				
Elective	–	1·0	1·0	1·0
Urgent (but planned)	–	1·4 (0·9, 2·1)	1·2 (0·8, 1·8)	1·1 (0·7, 1·8)
Emergency	–	1·5 (1·2, 2·0)	1·9 (1·4, 2·5)	2·0 (1·3, 3·0)
Surgery-related factors				
Day-care surgery	–	–	0·5 (0·3, 0·8)	0·5 (0·3, 0·9)
Surgery				
No	–	–	0·2 (0·1, 0·3)	0·1 (0·1, 0·3)
Minor	–	–	1·0	1·0
Major	–	–	2·0 (1·4, 2·7)	1·8 (1·3, 2·5)
Administrative factors				
Referral source				
Patient's initiative	–	–	–	0·5 (0·2, 1·0)
General practitioner	–	–	–	0·8 (0·6, 1·2)
Ambulance	–	–	–	1·3 (0·7, 2·3)
Consultant	–	–	–	1·0
Consultant elsewhere	–	–	–	1·0 (0·7, 1·5)
Other	–	–	–	1·0 (0·4, 2·4)
Route of admission				
Outpatient department	–	–	–	1·0
Emergency department	–	–	–	0·9 (0·6, 1·6)
Other department	–	–	–	1·5 (0·9, 2·6)
Other hospital	–	–	–	1·5 (0·9, 2·8)
Otherwise	–	–	–	0·7 (0·3, 1·9)

Values in parentheses are 95 per cent confidence intervals. *Currently smoking or stopped smoking < 1 year ago; †any form of dyspnoea or an abnormal chest radiograph; ‡serum creatinine ≥ 130 μmol/l, on dialysis or with renal transplant. AUC, area under the curve; ASA, American Society of Anesthesiologists

physical status, smoking behaviour, history of pulmonary disease, renal failure, diagnosis, urgency of admission, day-care surgery and extent of surgery.

In *Table 4* the odds ratios resulting from the logistic regression analysis of the models containing the nine prognostic variables with significant association ($P < 0{\cdot}15$) with a minor complication are given. Model 1 included the patient characteristics age, weight loss, ASA and pulmonary disease, and had an area under the curve of 0·62 (95 per cent c.i. 0·59 to 0·65). In model 2 the location of the disease was

Table 4 Multivariate analysis of area under receiver operating characteristic curve and odds ratios of variables significantly associated with a minor complication in four different models

	Model 1	Model 2	Model 3	Model 4
AUC	0·62 (0·59, 0·65)	0·63 (0·60, 0·66)	0·68 (0·65, 0·71)	0·69 (0·66, 0·73)
Odds ratios				
Patient-related factors				
Age (years)				
< 40	1·0	1·0	1·0	1·0
40–69	1·4 (1·1, 1·9)	1·4 (1·0, 1·9)	1·3 (1·0, 1·8)	1·3 (0·9, 1·8)
70–79	2·0 (1·3, 2·9)	1·9 (1·3, 2·9)	1·8 (1·2, 2·7)	1·8 (1·2, 2·7)
> 79	1·2 (0·7, 2·2)	1·1 (0·6, 2·1)	1·1 (0·6, 2·0)	1·2 (0·6, 2·2)
Major weight loss	1·9 (1·1, 3·2)	1·7 (1·0, 2·9)	1·6 (0·9, 2·8)	1·6 (0·9, 2·8)
ASA grade				
I	1·0	1·0	1·0	1·0
II	1·3 (0·9, 1·7)	1·3 (0·9, 1·8)	1·2 (0·9, 1·7)	1·2 (0·9, 1·7)
III	2·1 (1·4, 3·2)	2·1 (1·4, 3·2)	2·1 (1·3, 3·1)	2·2 (1·4, 3·4)
IV	1·5 (0·6, 3·7)	1·4 (0·6, 3·5)	1·6 (0·6, 4·1)	1·6 (0·6, 4·2)
V	4·7 (1·1, 20·3)	3·9 (0·9, 16·6)	3·4 (0·8, 15·0)	3·5 (0·8, 15·7)
Pulmonary disease*	1·6 (1·1, 2·3)	1·6 (1·1, 2·3)	1·4 (1·1, 2·5)	1·8 (1·2, 2·6)
Disease-related factors				
Central diagnosis	–	1·6 (1·2, 2·0)	1·7 (1·3, 2·2)	1·8 (1·4, 2·4)
Surgery-related factors:				
Day-care surgery	–	–	0·8 (0·5, 1·1)	0·8 (0·5, 1·2)
Surgery				
No	–	–	0·3 (0·2, 0·5)	0·3 (0·2, 0·5)
Minor	–	–	1·0	1·0
Major	–	–	1·4 (1·0, 1·8)	1·3 (0·9, 1·8)
Administrative factors				
Referral source				
Patient's initiative	–	–	–	0·8 (0·4, 1·6)
General practitioner	–	–	–	0·8 (0·5, 1·2)
Ambulance	–	–	–	1·7 (0·9, 3·0)
Consultant	–	–	–	1·0
Consultant elsewhere	–	–	–	1·1 (0·8, 1·7)
Other	–	–	–	1·5 (0·7, 3·1)
Route of admission				
Outpatient department	–	–	–	1·0
Emergency department	–	–	–	0·8 (0·5, 1·1)
Other department	–	–	–	1·0 (0·6, 1·9)
Other hospital	–	–	–	0·9 (0·5, 1·8)
Otherwise	–	–	–	0·7 (0·3, 1·8)

Values in parentheses are 95 per cent confidence intervals. *Any form of dyspnoea or an abnormal chest radiograph. AUC, area under the curve; ASA, American Society of Anesthesiologists

added and the area under the curve increased to 0·63 (95 per cent c.i. 0·60 to 0·66). The area under the curve of model 3 (inclusion of surgery-related variables) was 0·68 (95 per cent c.i. 0·65 to 0·71). Model 4, with all nine variables, had an area under the curve of 0·69 (95 per cent c.i. 0·66 to 0·72).

Discussion

The prediction of complications is an essential part of risk management in surgical practice. To recognize patients at high risk of developing a complication will contribute substantially to the quality and cost reduction of surgery. In the past other scoring systems have been used to predict complications. The ASA physical status classification was designed to standardize patient categories for uniform reporting but proved successful in predicting mortality[12,13] and to a lesser extent morbidity[14,15] in patients undergoing surgery. APACHE II has been developed to predict hospital mortality rate in groups of critically ill patients treated in the intensive care unit but has also been used as a scoring system in other surgical patients. It has value in predicting postoperative morbidity and mortality after major general surgical operations[15]. POSSUM has proved useful for comparative surgical audit[5,6], but seems to overestimate the

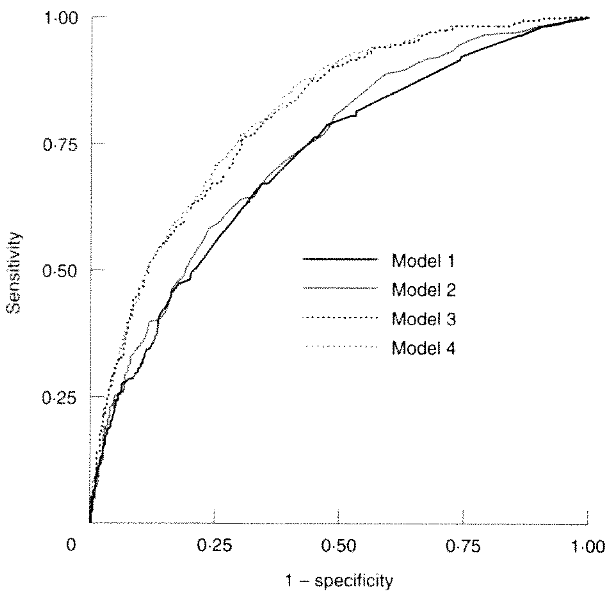

Fig. 1 Receiver operating characteristic curves for the different sets of variables. Model 1, patient-related factors (age, sex, weight loss, American Society of Anesthesiologists physical status, smoking behaviour, history of pulmonary disease and renal failure) (area under the curve (AUC) 0·69 (95 per cent confidence interval (c.i.) 0·67 to 0·72)); model 2, disease (diagnosis and urgency of admission)- and patient-related factors (AUC 0·72 (95 per cent c.i. 0·69 to 0·75)); model 3, surgery (complexity of surgery, whether day-care surgery)-, patient- and disease-related factors (AUC 0·79 (95 per cent c.i. 0·76 to 0·81)); model 4, all 13 significant variables (AUC 0·80 (95 per cent c.i. 0·77 to 0·82))

mortality rate when predicting outcome, especially in low-risk groups[16,17].

In a prospective survey Wolters *et al.*[18] tried to estimate the complication risk for an individual patient and found that they were unable to predict complications with any accuracy. It was the authors' view that a workable predictive model should be based on information that can be derived easily in all settings without extra effort in the majority of patients. Preoperative evaluation of most patients admitted to a surgical ward will consist of a history and physical examination without further investigations. The risk factors investigated in this model are readily available in all such patients.

A reliable model predicting complications can be based only on a (near) accurate incidence of complications. In this study, the recording of complications was done prospectively by both nurses and doctors, as part of daily rounds, and by a researcher especially assigned to the project. A complication rate of 23 per cent reflects the efficacy of the methods used. In other prospective studies, complication rates have varied between 2·7 and 34 per cent depending on the study population and on the methods and definitions used[3,7,14,15,18–28].

Not surprisingly, most known risk factors for the development of serious complications also proved influential in the present model. Increasing age was strongly associated with the risk of complications but, surprisingly, this risk declined for patients over 79 years of age. The most likely explanation for this phenomenon is a strong selection bias before hospitalization, with older high-risk patients not being considered suitable for admission or surgery.

Patients admitted for day-care surgery were half as likely to develop a minor complication and had one-fifth the risk of a serious complication compared with hospitalized patients. This supports the fact that day-care surgery is associated with less morbidity and that patients considered suitable for this type of surgery are properly selected. Nevertheless a considerable number of these patients develop a minor (7 per cent) or a serious (3 per cent) complication.

The variety of diagnoses at admission was successfully condensed to what might be considered most essential. If the diagnosis involved the central part of the body, the risk of a complication was almost twice as high as when the diagnosis involved a peripheral part.

As not all patients admitted to a surgical ward undergo surgery, it was necessary to develop a model that was applicable to all patients whether operated or not. Not unexpectedly, surgery was an important predictor for complications, especially serious ones. Using minor surgery as the reference group, patients undergoing major surgery had an almost twofold risk of developing a serious complication whereas patients admitted for observation, investigation or medical treatment had only one-tenth the risk. This association was less strong for minor complications. The power of the predictive model increased substantially after adding surgery-related factors. The model derived can predict a serious complication correctly in 79 of 100 patients. Unfortunately, the predictive ability (area under the ROC curve 0·69) of the model (4) for minor complications was not high enough for practical use. Although the impact of a minor complication for the individual patient should not be underestimated, serious complications may constitute a real threat to a patient's life and should be taken into account carefully before deciding whether or not to operate.

A further advantage of the model is the potential application of the risk score, in comparison of outcome and performance assessment in surgery[12–17].

Appendix

The risk of a patient developing a serious complication can be calculated using the following formula:

$$P = 1/(1 + e^{-Z})$$

Z can be calculated with the following equation:

$$Z = -3{\cdot}6739 + (0{\cdot}5518 \times a1) + (0{\cdot}7855 \times a2) + (0{\cdot}4343 \times a3) + (0{\cdot}3216 \times b) + (-0{\cdot}7485 \times c) + (0{\cdot}2080 \times d1) + (0{\cdot}6327 \times d2) + (0{\cdot}6761 \times f) + (0{\cdot}6102 \times g) + (0{\cdot}2889 \times h1) + (0{\cdot}7382 \times h2) + (0{\cdot}7526 \times h3) + (1{\cdot}2826 \times h4) + (0{\cdot}2940 \times i) + (0{\cdot}6444 \times j) + (0{\cdot}3668 \times k) + (-1{\cdot}8841 \times l1) + (0{\cdot}6699 \times l2)$$

where $a1 = 1$ if 40–69 years, otherwise $a1 = 0$; $a2 = 1$ if 70–79 years, otherwise $a2 = 0$; $a3 = 1$ if 79 years or more, otherwise $a3 = 0$;
$b = 1$ if male and $b = 0$ if female;
$c = 1$ if day-care surgery, otherwise $c = 0$;
$d1 = 1$ if urgent (but planned), otherwise $d1 = 0$; $d2 = 1$ if emergency, otherwise $d2 = 0$;
$f = 1$ if diagnosis central, otherwise $f = 0$;
$g = 1$ if patient lost more than 10 per cent of body-weight during previous 3 months, otherwise $g = 0$;
$h1 = 1$ if ASA II, otherwise $h1 = 0$; $h2 = 1$ if ASA III, otherwise $h2 = 0$; $h3 = 1$ if ASA IV, otherwise $h3 = 0$; $h4 = 1$ if ASA V, otherwise $h4 = 0$;
$i = 1$ if smokes (currently smoking or stopped smoking less than 1 year ago), otherwise $i = 0$;
$j = 1$ if pulmonary disease present (any form of dyspnoea or an abnormal chest radiograph), otherwise $j = 0$;
$k = 1$ if renal failure (serum creatinine 130 µmol/l or greater, on dialysis or with renal transplant), otherwise $k = 0$;
$l1 = 1$ if no surgery, otherwise $l1 = 0$; $l2 = 1$ if major surgery, otherwise $l2 = 0$.

Examples

The risk of the reference patient developing a serious complication is 2 per cent. The reference patient is a female, younger than 40 years of age, treated with elective, minor non-day-care surgery, for a diagnosis not involving the central part of the body. She is a patient without major weight loss, classified as ASA I, who does not smoke, have pulmonary disease or renal failure.

An otherwise healthy, non-smoking 82-year-old man with a ruptured aneurysm of the abdominal aorta has a 58 per cent risk of a serious complication ($a3 = 1$, $b = 1$, $d2 = 1$, $f = 1$, $h4 = 1$, $l2 = 1$ and all other variables are 0). This risk increases to 84 per cent if he smokes and has pulmonary and renal disease ($a3 = 1$, $b = 1$, $d2 = 1$, $f = 1$, $h4 = 1$, $i = 1$, $j = 1$, $k = 1$, $l2 = 1$ and other variables are 0).

A 62-year-old female smoker with pulmonary disease (ASA II) admitted for elective laparoscopic cholecystectomy has an 18 per cent risk of a serious complication ($a1 = 1$, $f = 1$, $h1 = 1$, $j = 1$ and all other variables are 0).

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Original article

Time course of peritoneal tissue plasminogen activator after experimental colonic surgery: effect of hyaluronan-based antiadhesive agents and bacterial peritonitis

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Background: This study assessed the peritoneal fibrinolytic response during the first week after colonic surgery in rats with and without bacterial peritonitis, and possible modulation of the response by two hyaluronan-based antiadhesive agents.

Methods: A colonic anastomosis was constructed in 90 male Wistar rats. Peritonitis was induced in another 108 rats and a colonic anastomosis was constructed after 24 h. Rats in both groups were randomized into an untreated group or one of two groups treated with hyaluronan-based agents. One-third of each group was killed at each of days 1, 3 and 7 after operation, and tissue plasminogen activator (tPA) antigen and activity were measured in peritoneal biopsies.

Results: One day after colonic surgery in normal rats, tPA antigen concentration was significantly ($P < 0{\cdot}005$) increased, whereas tPA activity levels were normal. By day 3 after operation tPA antigen had returned to baseline values while tPA activity was significantly increased ($P < 0{\cdot}05$). One day after inducing peritonitis tPA antigen was significantly increased ($P < 0{\cdot}001$), while tPA activity was significantly reduced ($P < 0{\cdot}05$). Three and seven days after colonic surgery in rats with peritonitis tPA activity was increased ($P < 0{\cdot}001$) while tPA antigen had returned to baseline values. Neither of the hyaluronan-based agents affected peritoneal tPA antigen levels or activity after colonic surgery.

Conclusion: Both abdominal surgery and infection caused an early increase in peritoneal tPA antigen levels, followed by an increase in tPA activity. Peritonitis severely depressed early tPA activity. Application of hyaluronan-based agents did not affect the peritoneal fibrinolytic response to surgery and/or infection.

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Introduction

Damage to the peritoneum from abdominal surgery or intra-abdominal infection is accompanied by peritoneal inflammation, including fluid exudation into the abdominal cavity. This exudate is rich in fibrinogen, which is processed into fibrin as the result of an activated coagulation cascade. Fibrin deposits may become organized by fibroblast ingrowth and neovascularization, and form fibrous adhesions. In infectious conditions, fibrin deposits may become a nidus for abscesses. The peritoneal fibrinolytic system is crucial in preventing fibrin deposition and subsequent adhesion and abscess formation. It is generally accepted that intra-abdominal adhesions and abscesses do not form if fibrin is lysed within the first week after the peritoneal insult.

The balance between plasminogen activators and inhibitors in the peritoneal cavity is thought to determine fibrin degradation[1]. Tissue-type plasminogen activator (tPA) is the main plasminogen activator; its activity is restricted by plasminogen activating inhibitors (PAIs), predominantly type 1 (PAI-1). Reduced fibrinolytic activity after abdominal surgery and during peritonitis has been demonstrated in peritoneum in both clinical and experimental studies[2–7]. An increase in the expression of PAI in the peritoneal cavity is held responsible for the low fibrinolytic activity. An intraoperative reduction in tPA levels, however, has also been described[3,7].

Mechanistically, the results of clinical studies have limited value because the balance between plasminogen activators and inhibitors may be assessed only during surgery or at single time points after an injury, such as peritonitis. Collection of sequential peritoneal biopsies to obtain an accurate insight into peritoneal fibrin-degrading capacity during the first postoperative week is not feasible in patients. Few animal studies have measured sequential peritoneal fibrinolytic activity with time[4,8,9]. These studies, however, hardly mimic the clinical situation of abdominal surgery and peritonitis.

Hyaluronan-based agents reduce intra-abdominal adhesions after abdominal surgery[10–12]. Hyaluronate solution reduces intra-abdominal adhesion and abscess formation in an infectious environment[13]. Hyaluronan has a documented biological activity, including a regulatory role in inflammation, cell proliferation and cell locomotion[14,15]. Of particular interest in the context of fibrin resolution is the recent observation that sodium hyaluronate influenced the fibrinolytic properties of mesothelial cells in the presence of proinflammatory stimuli[16].

The aim of this study was to assess the time course of fibrinolytic activity in an experimental model that mimicked colonic resection with and without peritonitis during the first week after operation. In addition, the effect of clinically used hyaluronan-based antiadhesive agents on fibrinolytic activity was investigated.

Materials and methods

Study design

Male Wistar rats (Harlan Nederland, Zeist, The Netherlands) were allowed to acclimatize to laboratory conditions for 1 week before experiments. Animals were housed at 21°C with a day–night cycle of 12 h. They had free access to water and standard rodent chow (Hope Farms, Woerden, The Netherlands). Body-weight was measured immediately before the operation and at the time of death. The Animal Ethics Review Committee of the Faculty of Medicine, University of Nijmegen, approved the study protocol.

Experiment 1: colonic surgery

Ninety rats, weighing between 250 and 300 g, were anaesthetized with a mixture of Fluothane (Zeneca, Macclesfield, UK), nitrous oxide and oxygen. The abdomen was shaved, disinfected with 70 per cent alcohol and opened via a 3-cm midline incision. The descending colon was dissected and a 1-cm segment was resected 3 cm proximal to the peritoneal reflection. Subsequently, an inverted single-layer end-to-end anastomosis was constructed with eight interrupted sutures of 8/0 monofilament material (Ethicon, Norderstedt, Germany). Animals were randomized into three groups of 30 each. Rats in the first group received no treatment. In the second group a 1 × 3-cm hyaluronate–carboxymethylcellulose bioresorbable membrane (Seprafilm®; Genzyme, Cambridge, Massachusetts, USA) was wrapped around the anastomosis and a 3 × 4-cm piece of the same material was left under the midline incision. In the third group, the abdominal cavity was coated with 3 ml 0·4 per cent hyaluronate solution (Sepracoat™; Genzyme) before any manipulation of the viscera and, after completion of the anastomosis, another 5 ml hyaluronate solution was instilled in order to fill the abdominal cavity. The abdomen was closed in two layers using a 3/0 polyglactin suture (Ethicon) for the fascia and staples for the skin. After operation, the rats were resuscitated with 10 ml saline subcutaneously. One-third of the animals in each group were killed, by carbon dioxide asphyxiation, on days 1, 3 and 7 after operation, and parietal peritoneal biopsies of approximately 1 × 1 cm were taken in the left lower quadrant near the site of surgical trauma by sharp dissection, not using cautery.

Experiment 2: colonic surgery under septic conditions

In 108 rats, weighing between 250 and 320 g, bacterial peritonitis was induced using a caecal ligation and puncture model as described previously[13,17]. Briefly, the caecum was dissected through a 3-cm midline laparotomy under anaesthesia and was filled backwards with faeces. Thereafter, the caecum was ligated next to the ileocaecal valve and punctured once with a 19-G needle at the antimesenteric side. Immediately after abdominal closure, rats received a single dose of gentamicin (Centrafarm Services, Etten-Leur, The Netherlands) 6 mg per kg body-weight intramuscularly and buprenorphine (Temgesic®; Reckitt and Colman, Amstelveen, The Netherlands) 0·1 mg per kg body-weight subcutaneously. All animals were resuscitated with 10 ml saline subcutaneously. After 24 h, the abdomen was reopened, the ligated caecum was resected and a colonic end-to-end anastomosis was constructed. Animals were randomized into three groups (36 in each): an untreated group, a group treated with hyaluronate–carboxymethylcellulose bioresorbable membrane and a group treated with 0·4 per cent hyaluronate solution, as described above. One-third of the animals in each group were killed on days 1, 3 and 7 and parietal peritoneal biopsies were collected as described above.

Baseline values

Peritoneal biopsies from the left lower abdomen were taken from ten rats to obtain baseline values. In 12 rats peritonitis was induced as described above. These rats were killed after 24 h and peritoneal biopsies were taken to obtain values after 24 h of peritoneal infection (day 0 after surgery).

Tissue sampling and processing

The peritoneum was dissected carefully taking care not to include the underlying muscle. The tissue specimens were snap-frozen in liquid nitrogen and stored at –70°C until further processing. Before homogenizing, a sample of thawing peritoneal tissue was removed, blotted and weighed. Each biopsy was rinsed with phosphate-buffered saline (PBS) containing sodium chloride 0·5 mol/l (pH 7·4), cut into small pieces and placed into ice-cold homogenization buffer (PBS with 0·01 per cent Triton X-100 (Sigma, St Louis, Missouri, USA)) at a final concentration of 40 mg tissue per ml buffer. The tissue was homogenized for 60 s on ice using a Polytron homogenizer (Ultra Thurrax IKA T-25; Janke and Kunkel, Staufen, Germany), centrifuged at 10 000*g* for 4 min at 4°C, and the supernatant was stored at – 70°C until further analysis. Tissue processing and assays were done in batches.

Measurement of tissue-type plasminogen activator activity

Activity of tPA in the tissue homogenate was measured using monoclonal antibodies that do not block the active site of tPA. Microtitre plates were coated for 16 h with a monoclonal rabbit antirat tPA antibody (AD 1120; American Diagnostica, Greenwich, Connecticut, USA) in a coating buffer (antibody concentration 5 µg/ml) containing sodium phosphate 10 mmol/l and sodium chloride 145 mmol/l, pH 7·2. Afterwards, the plates were washed twice with buffer (sodium phosphate 10 mmol/l, sodium chloride 145 mmol/l, pH 7·2, containing 0·05 per cent (w/v) Tween 20 (Merck, Darmstadt, Germany)) and incubated for 1 h with bovine serum albumin (10 g/l) (BSA Fraction V; Sigma) to avoid unspecific binding. After washing, samples and reference tPA (Novo Nordisk, Bagsvaerd, Denmark) were incubated for 1 h. The reaction mixture, consisting of Tris 0·5 mol/l, pH 8·3, 0·01 per cent Triton X-100, Flavigen™Pli 1·1 mmol/l (Biopool, Umeå, Sweden), Glu-plasminogen 110 µg/ml prepared from human plasma and fibrinogen fragment 150 µg/ml, was added. Plates were incubated overnight at room temperature. Active tPA converted the inactive zymogen plasminogen yielding active plasmin, which subsequently cleaved the Flavigen™Pli, releasing the yellow product paranitroanaline which was measured spectrophotometrically at 405 nm.

Measurement of tissue-type plasminogen activator antigen

An enyme-linked immunosorbent assay[18] was used to measure tPA antigen in the tissue homogenate. Briefly, microtitre plates were coated with rabbit antirat tPA immunoglobulin (Ig) G (4 µl/ml in carbonate buffer, pH 9·0) overnight at 4°C and washed. Samples (diluted in PBS containing casein 5 mg/ml) were incubated overnight at 4°C and washed. Bound tPA antigen was subsequently quantified using biotinylated rabbit antirat tPA IgG, followed by avidin–peroxidase and tetramethylbenzidine. Rat tPA purified from L_2 cells (0·5–4·0 ng/ml) was used as standard. The rat L_2 tPA had been calibrated against recombinant rat JMI-229 tPA.

Statistical analysis

Values are given as mean(s.d.). Analysis of differences between postoperative days, and between hyaluronate-treated groups and untreated groups, was performed using analysis of variance followed by Fisher's post-hoc tests.

Results

Experiment 1: colonic surgery

No significant differences in body-weight were observed between untreated rats and those treated with 0·4 per cent hyaluronate solution or hyaluronate–carboxymethylcellulose bioresorbable membrane.

During the experiment one rat (3 per cent) with hyaluronate–carboxymethylcellulose bioresorbable membrane died prematurely from anastomotic dehiscence.

Tissue-type plasminogen activator antigen

Some 24 h after colonic surgery a 1·5-fold increase in tPA antigen concentration was measured compared with baseline levels ($P = 0·001$) (*Fig. 1*). A significant decline was observed, approaching baseline concentrations at day 3 after operation ($P < 0·001$ *versus* day 1), and below baseline levels at day 7 ($P = 0·02$ *versus* day 3).

Tissue-type plasminogen activator activity

Peritoneal tPA activity was within the baseline range 24 h after colonic surgery, but a 25 per cent increase was

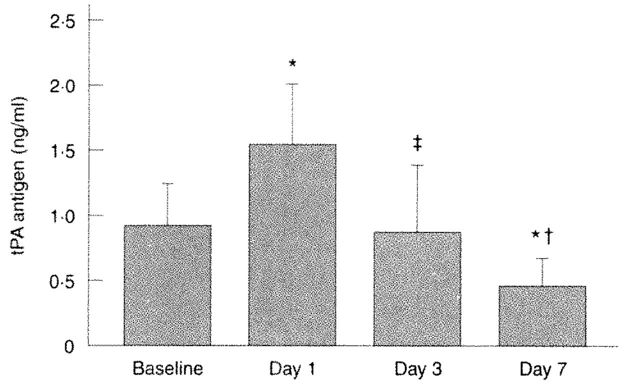

Fig. 1 Tissue-type plasminogen activator (tPA) antigen level in the parietal peritoneum after colonic surgery in normal rats. Values are mean(s.d.). **P* < 0·01 *versus* baseline; †*P* < 0·05 *versus* day 3; ‡*P* < 0·001 *versus* day 1 (analysis of variance followed by Fisher's post-hoc tests)

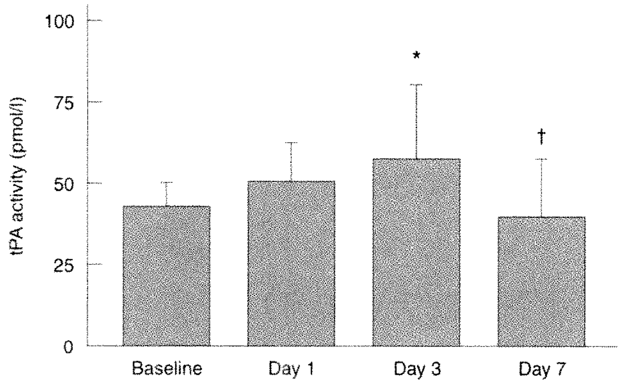

Fig. 2 Tissue-type plasminogen activator (tPA) activity in the parietal peritoneum after colonic surgery in normal rats. Values are mean(s.d.). **P* < 0·05 *versus* baseline; †*P* < 0·01 *versus* day 3 (analysis of variance followed by Fisher's post-hoc tests)

measured at day 3 (*P* = 0·03) (*Fig. 2*). By day 7, tPA activity had significantly declined in comparison to that at day 3 (*P* < 0·01), returning to baseline levels.

Effect of hyaluronate-based agents

Neither hyaluronate–carboxymethylcellulose bioresorbable membrane nor hyaluronate solution significantly affected tPA antigen concentration or tPA activity at any time point measured (*Table 1*).

Experiment 2: colonic surgery under septic conditions

Body-weight did not significantly differ between untreated rats and those treated with hyaluronan compounds.

Table 1 Tissue-type plasminogen activator antigen level and activity in peritoneal biopsies 1, 3 and 7 days after colonic surgery in normal rats

	Day 1	Day 3	Day 7
tPA antigen (ng/ml)			
Control	1·54(0·47)	0·88(0·51)	0·47(0·21)
HA-CMC	1·85(0·77)	1·14(0·37)	0·52(0·24)
HA solution	1·55(0·28)	1·00(0·63)	0·45(0·19)
tPA activity (pmol/l)			
Control	50·7(12·0)	58·0(22·7)	40·1(8·0)
HA-CMC	48·6(14·4)	68·1(48·0)	41·7(12·0)
HA solution	50·7(12·7)	47·0(17·9)	43·2(7·7)

Values are mean(s.d.). Rats were treated with either hyaluronate–carboxymethylcellulose (HA-CMC) bioresorbable membrane or 0·4 per cent hyaluronate (HA) solution. Controls received no treatment

One day after caecal ligation and puncture all rats had developed peritonitis with fibrous exudate and pus in the peritoneal cavity. They exhibited symptoms of sepsis including apathetic behaviour, ocular exudates, piloerection and diarrhoea. These symptoms resolved within 2 days after removing the ligated and perforated caecum.

Eighteen (15 per cent) of 120 rats died prematurely. Two rats died immediately after anaesthesia on the day of caecal ligation and puncture. Fourteen rats died on the first day after performing the colonic anastomosis. The remaining two died on days 2 and 3. There was no significant difference in mortality rate between the groups. In all rats septicaemia caused by caecal ligation and puncture was the cause of death.

Tissue-type plasminogen activator antigen

On the day of operation (1 day after induction of bacterial peritonitis; day 0) a 2·5-fold increase in tPA antigen levels was observed compared with baseline values (*P* < 0·001). The levels remained high on day 1, 24 h after colonic surgery (*Fig. 3*). By day 3 after surgery there was a significant decline (*P* = 0·03 *versus* day 1) towards baseline levels, and a similar level was observed at day 7.

Tissue-type plasminogen activator activity

On the day of operation (day 0) a sixfold decrease in tPA activity was measured compared with baseline (*P* = 0·04) (*Fig. 4*). One day later, tPA activity had returned to baseline levels and a 3·5-fold increase was observed at day 3 compared with baseline (*P* < 0·001). By day 7, tPA activity was lower than that at day 3 (*P* = 0·02), but remained significantly higher than the baseline activity (*P* < 0·001).

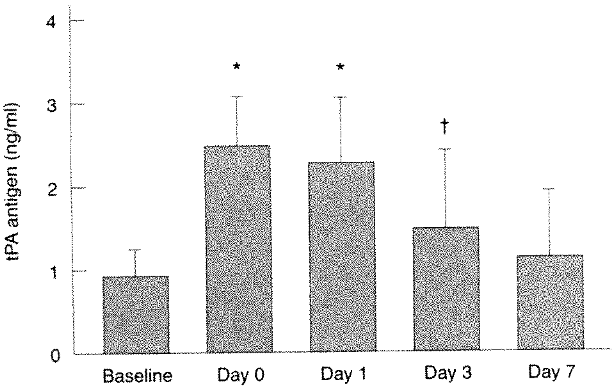

Fig. 3 Tissue-type plasminogen activator (tPA) antigen level in the parietal peritoneum after colonic surgery in rats with experimental peritonitis. Values are mean(s.d.). $*P < 0{\cdot}001$ *versus* baseline; $\dagger P < 0{\cdot}05$ *versus* day 1 (analysis of variance followed by Fisher's post-hoc tests)

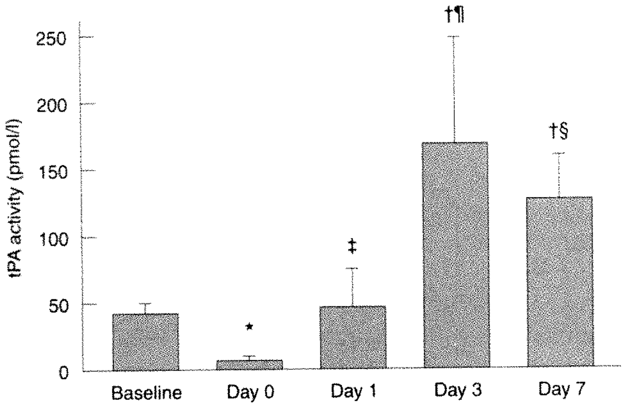

Fig. 4 Tissue-type plasminogen activator (tPA) activity in the parietal peritoneum after colonic surgery in rats with experimental peritonitis. Values are mean(s.d.). $*P < 0{\cdot}05$, $\dagger P < 0{\cdot}001$ *versus* baseline; $\ddagger P < 0{\cdot}05$ *versus* day 0; $\S P < 0{\cdot}05$ *versus* day 3; $\P P < 0{\cdot}001$ *versus* day 1 (analysis of variance followed by Fisher's post-hoc tests)

Effects of hyaluronate-based agents

In accordance with the findings in rats without peritonitis, treatment with hyaluronate–carboxymethylcellulose bioresorbable membrane or hyaluronate solution did not affect tPA antigen concentration (*Table 2*). Treatment with hyaluronate–carboxymethylcellulose bioresorbable membrane significantly depressed tPA activity 1 day after colonic surgery ($P = 0{\cdot}01$). At day 3 and day 7 after colonic surgery there was no significant difference between rats treated with either hyaluronate–carboxymethylcellulose bioresorbable membrane or hyaluronate solution and untreated rats (*Table 2*).

Table 2 Tissue-type plasminogen activator antigen level and activity in peritoneal biopsies 1, 3 and 7 days after colonic surgery in rats with experimental peritonitis

	Day 1	Day 3	Day 7
tPA antigen(ng/ml)			
Control	2·26(0·80)	1·47(0·94)	1·23(0·80)
HA-CMC	2·35(0·54)	1·43(0·80)	0·96(0·64)
HA solution	2·40(0·46)	0·91(0·53)	0·70(0·52)
tPA activity (pmol/l)			
Control	46·9(28·4)	168·2(79·3)	126·8(32·5)
HA-CMC	21·4(18·9)*	197·5(85·4)	133·0(75·7)
HA solution	32·0(14·0)	210·0(70·7)	138·6(40·7)

Values are mean(s.d.). Rats were treated with either hyaluronate–carboxymethylcellulose (HA-CMC) bioresorbable membrane or 0·4 per cent hyaluronate (HA) solution. Controls received no treatment.
$*P < 0{\cdot}05$ *versus* control (analysis of variance followed by Fisher's post-hoc tests)

Discussion

In the present study the peritoneal fibrinolytic capacity during the first week after colonic surgery was assessed in rats with and without bacterial peritonitis by measuring the key fibrinolytic factor tPA. The results demonstrated that the tPA antigen content in peritoneal tissue was increased in the early phase after colonic surgery, both under non-infective and infective conditions. However, the early increase in tPA antigen did not result in an increased fibrinolytic activity, as measured by tPA activity. The reason for this discrepancy between tPA expression and activity cannot be elucidated from the present observations, but is likely to be related to inhibition of plasminogen activity. The use of hyaluronan-based antiadhesive derivatives influenced neither peritoneal tPA antigen nor activity. Their antiadhesive properties did not seem to be mediated by modulation of fibrinolytic activity *in vivo*.

Clinical studies on the peritoneal fibrinolytic response using sequential biopsies collected during laparotomy showed an early decrease in tPA antigen concentration, implying that tPA expression was decreased during surgery[3,7]. Sampling the peritoneal fluid 24 h after elective surgery in patients also revealed reduced tPA antigen levels[6]. In contrast, in the present study there was an early increase in tPA antigen, indicating that the fibrinolytic potential in the peritoneum was preserved or even stimulated after injury. This difference may be explained by the longer time interval between injury and measurement in the present study.

In addition, the composition of the peritoneal biopsy may have contributed to the different observations. In rats it is impossible to prevent taking submesothelial tissue, which is rich in endothelium and an important source of tPA. In humans thinner biopsies can be taken that include the peritoneum only. The significance of the presence of any underlying peritoneal tissue to peritoneal fibrinolytic activity has not been investigated, but it seems likely from, for example, the peritoneal route of inflammatory mediators that it does play a role.

The return to baseline values of tPA 3 days after surgery was surprising since it was anticipated that this interval would coincide with that of mesothelial cells repopulating the peritoneal areas of injury and producing large amounts of tPA, resulting in a steady tPA increase in peritoneal biopsies[19].

The early increase in tPA did not result in enhanced tPA activity, which is associated with fibrinolysis. Indeed, intra-abdominal infection reduced tPA activity, probably due to high concentrations of PAI. Currently, there is no commercially available assay for the detection of rat PAI-1 to demonstrate this. This pattern of tPA activity resembled that shown by Vipond *et al.*[8], who induced both a chemical and bacterial peritonitis in rats. They did not, however, demonstrate such a clear rebound phenomenon of tPA activity, probably because their model involved a less severe peritonitis. In contrast to the present findings, Bakkum *et al.*[9] showed increased tPA activity up to 1 month after surgical injury in rats. Their model was more likely to represent healing of large peritoneal defects including abdominal wall muscles than smaller peritoneal injury. Heavily vascularized scar tissue was held responsible for the sustained increase in tPA activity. Increased tPA activity was found 7 days after bacterial peritonitis in the present investigation, corresponding with hyperaemia and persistent inflammation owing to the presence of residual abscesses.

The fact that the present data showed that plasminogen activator levels changed during the first week after injury may have implications for the timing of interventions that enhance fibrin degradation and prevent formation of adhesions and abscesses. Increasing tPA activity in the first 48 h seems more appropriate than increasing it later. This was supported by early findings of McRitchie *et al.*[20] that delayed administration of tPA was less effective in resolving infected fibrin clots in the abdominal cavity than early administration.

The use of hyaluronan-based antiadhesive derivatives neither influenced peritoneal tPA antigen nor its activity. Thus, the antiadhesive capacity did not seem to be related to increased peritoneal fibrinolysis. This is seemingly in contrast to a previous study, in which it was demonstrated that sodium hyaluronate enhanced tPA antigen production of cultured human peritoneal mesothelial cells[16]. Mesothelial cells, however, may have been absent in the peritoneal biopsies, especially early during inflammation[4,19]. Furthermore, tPA antigen may have been upregulated following the peritoneal insult, and an additional stimulating effect might not be observed.

Based on these experiments, future clinical studies are warranted on the balance between activators and inhibitors of fibrinolysis during the process of peritoneal inflammation and subsequent repair. Newly developed techniques of continuous sampling of the peritoneal microenvironment, including an implantable microchamber[21], may be useful in elucidating this complex process of peritoneal repair.

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Original article

Risk-adjusted surgical audit with the POSSUM scoring system in a developing country

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Background: The Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) is an objective and appropriate scoring system for risk-adjusted comparative general surgical audit. This score was devised in the UK and has been used widely, but application of POSSUM to centres outside the UK has been limited, especially in developing countries. This prospective study validated its application in a surgical practice with a different population and level of resources.

Methods: All general surgical patients who were operated on under regional or general anaesthesia as inpatients over a 4-month period at Sarawak General Hospital in 1999 were entered into the study. All data (12 physiological and six operative factors) were analysed for mortality only with the POSSUM equation and the modified Portsmouth POSSUM (P-POSSUM) equation. Comparisons were made between predicted and observed mortality rates according to four groups of risk: 0–4, 5–14, 15–49 and 50 per cent or more using the 'linear' method of analysis.

Results: There were 605 patients who satisfied the criteria for the study. Some 56·7 per cent of patients were in the lowest risk group. The POSSUM predictor equation significantly overestimated the mortality in this group, by a factor of 9·3. The overall observed mortality rate was 6·1 per cent and, again, the POSSUM predictor equation overestimated it at 10·5 per cent ($P < 0{\cdot}01$). In contrast, the observed and predicted mortality rates for all risk groups, including the predicted overall mortality rate of 4·8 per cent, were comparable when the P-POSSUM predictor equation was used.

Conclusion: The POSSUM scoring system with the modified P-POSSUM predictor equation for mortality was applicable in Malaysia, a developing country, for risk-adjusted surgical audit. This scoring system may serve as a useful comparative audit tool for surgical practice in many geographical locations.

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Introduction

Comparative audits using crude morbidity and mortality rates have obvious limitations[1,2]. Various scoring systems with risk-adjusted rates have been developed to overcome these deficiencies. A recent review of the scoring systems relevant to general surgical practice concluded that the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) was the most appropriate of the currently available scores[3].

The POSSUM scoring system was first described by Copeland *et al.*[4] in 1991. Twelve physiological and six operative factors were developed for scoring and these scores were applied to an equation to obtain a predicted mortality rate for each patient. The observed rate was compared with the predicted rate for evaluation. Evaluation of the POSSUM surgical scoring system revealed overestimation of mortality rate in the lowest risk group[5,6]. A modification to the predictor equation was subsequently published as the Portsmouth POSSUM (P-POSSUM) equation[6]. This P-POSSUM equation was claimed to produce a closer fit with the observed in-hospital mortality rate in low-risk groups. POSSUM methodology has found applications in general surgical[4–6], colorectal[7], gastrointestinal[8], vascular[9,10] and thoracic[11] patients.

Application of the POSSUM scoring system in developing countries, where the level of healthcare and resources differs, is limited. Despite these differences, POSSUM is likely to be applicable in this local setting as surgical practice in Malaysia is similar to that in the UK. To test the possible suitability of POSSUM as a comparative audit tool, a prospective study at the largest public hospital in Sarawak was carried out. If validated, this scoring system would be a useful comparative auditing tool to assess the quality of surgical care in this region.

Patients and methods

A prospective study was carried out for 4 consecutive months (July to October 1999) at the Sarawak General Hospital after an initial trial of 2 months. Sarawak General Hospital is the largest public hospital and the referral centre for the Malaysian state of Sarawak, with a total population of about 2 million. At the time of the study all the surgeons were trained and qualified from one of the royal colleges of the UK, Australasia or India.

All patients over the age of 12 years who underwent operation under general or regional anaesthesia were included. Patients who had day-case surgery and/or operation under local anaesthesia were excluded from the study as complication and mortality rates were extremely low and follow-up was incomplete owing to social and geographical constraints.

The original morbidity equation proposed in the POSSUM scoring system was not used because of difficulties involved in defining morbidity, which was observer dependent. Furthermore, many patients were discharged to rural areas where reviews were conducted at local clinics. Death in hospital or within 30 days of operation was used as the endpoint of the study.

All consecutive cases were identified daily and scored as described by Copeland *et al.*[4] before operation using the 12 physiological factors and at the end of the operation using the six operative factors. All data were recorded manually on printed forms and subsequently transferred to Microsoft Excel® (Microsoft Corporation, Washington, District of Columbia, USA) for analysis. The risk of death, R, was calculated using the POSSUM[4] and P-POSSUM[6] equations as follows:

POSSUM $\ln[R/(1 - R)] = - 7{\cdot}04 + (0{\cdot}13 \times \text{physiological score}) + (0{\cdot}16 \times \text{operative score})$

P-POSSUM $\ln[R/(1 - R)] = - 9{\cdot}065 + (0{\cdot}1692 \times \text{physiological score}) + (0{\cdot}1550 \times \text{operative score})$

Four sizes of risk range were chosen to give meaningful comparison between predicted and observed deaths. These were assessed with the χ^2 test; $P < 0{\cdot}05$ was considered statistically significant. The 'linear' method of analysis was used rather than 'exponential' analysis because it was more straightforward and simpler[9].

Results

A total of 605 patients was analysed over the period. The overall observed mortality rate was 6·1 per cent. The types of surgical procedure performed are shown in *Table 1*.

Comparison between predicted and observed rates of mortality using both POSSUM and P-POSSUM equations was performed and analysed with the linear method. *Table 2*

Table 1 Types of surgical procedure performed in the 605 patients

	No. of procedures
General (abdominal, endocrine and breast)	435
Urological	67
Reconstructive and vascular	36
Neurosurgical and miscellaneous	67

Table 2 Comparison of observed and predicted deaths with the POSSUM equation

	No. of patients	Mortality rate (%)		Observed: predicted ratio
		Predicted	Observed	
Risk of death (%)				
0–4	343	2·7	0·3	0·11*
5–14	146	8·3	5·5	0·66
15–49	93	28·4	18·3	0·64
⩾ 50	23	68·0	47·8	0·70
Total	605	10·5	6·1	0·58*

POSSUM, Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity. $^*P < 0{\cdot}01$ (χ^2 test)

Table 3 Comparison of observed and predicted deaths with the P-POSSUM equation

	No. of patients	Mortality rate (%)		Observed: predicted ratio
		Predicted	Observed	
Risk of death (%)				
0–4	494	1·2	1·8	1·49
5–14	59	9·1	18·6	2·06
15–49	43	27·0	30·2	1·12
⩾ 50	9	67·3	44·4	0·66
Total	605	4·8	6·1	1·28

P-POSSUM, Portsmouth Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity shows the comparison results when the original POSSUM equation was applied to this group of patients. This equation resulted in a 1·7-fold overestimation of overall mortality. In particular, mortality was overpredicted by a factor of 9·3 in the lowest risk group (0–4 per cent), which constituted 56·7 per cent of the patients.

Table 3 shows the application of the P-POSSUM equation to this same group of patients. There was a close fit with the observed mortality in all risk groups, and no statistical differences in the comparison.

Discussion

POSSUM was developed as an adjunct to surgical audit to allow assessment of the 'quality' of care[4]. It allows comparison of the audits of different patient populations by taking into account variations in the physiological condition of patients at operation and the extent of surgical intervention or severity of operation. This has enabled application to data sets with a different case mix.

Whiteley *et al.* proposed in their initial study[5] that geographical comparison of the use of POSSUM would be welcome. Their subsequent paper[6] and studies by other workers[8,10] in the UK used the modified P-POSSUM equation and concluded that P-POSSUM works independently of geographical location. This is not surprising as the POSSUM system was devised from logistic regression of data from surgical patients in the UK where fairly uniform surgical practice might be expected.

Application of the POSSUM scoring system outside UK practice is limited. This study shows that the POSSUM scoring system with the P-POSSUM predictor equation for deaths is equally applicable in Malaysia. The range of surgical procedures was similar to that reported in the original POSSUM study[4] and exclusion criteria were as in the P-POSSUM study[6]. In Malaysia most surgical specialists continue to train within the UK system and obtain postgraduate qualifications from all the UK surgical royal colleges. A further period of supervised training of at least 18 months after the date of the 'fellowship' by senior surgeons is required before recognition as a general clinical specialist. Until recently, many senior surgeons were trained in the UK. With similar foundations of surgical practice, a scoring system such as POSSUM should be applicable in this local setting despite some differences in resources and level of healthcare.

POSSUM does not take into consideration certain factors that may have an impact on surgical care and outcome such as surgical experience and seniority, anaesthetic expertise, duration of operation, organ system being operated on and duration of stay after operation. In the study from the University of Otago[12], logistic regression analysis showed that duration of operation, operation category, inpatient status (operative stay) and organ system in which the procedure was carried out were the strongest predictors of postoperative morbidity. Although not directly comparable, the operative severity score components of POSSUM, such as total blood loss, peritoneal soiling, presence of malignancy, number of procedures and operative severity score, indirectly reflect the duration of operation, affect the postoperative stay and the organ system operated on. Surgical expertise may influence the amount of blood loss and peritoneal soiling. Despite these apparent deficiencies, the POSSUM scoring system with the P-POSSUM equation for mortality produced a close fit, and the contribution of these variables to mortality might not be as significant as that to morbidity.

As with other investigators[5,6,8,10], application of the original POSSUM equation to this series of patients yielded a poor performance for the study of mortality. It overestimated the overall mortality by a factor of 1·7 and mortality in the lowest risk group by 9·3-fold. This group formed the majority of surgical patients and this overestimation would be mistaken as exceptional surgical results if not interpreted properly. However, such poor performance of the scoring system may well be due to the methodology of analysis, as pointed out by Wijesinghe *et al.*[9]. The comparative analysis using the POSSUM equation requires a more complex 'exponential' method to give an accurate mortality prediction of the whole population studied. In addition, it is unclear how subgroup analysis can be performed by this method. Although the 'exponential' method of analysis and subgroup analysis were not clearly described in the original POSSUM publication[4], the former was later clarified[9].

In comparison, the P-POSSUM equation produced a close fit between the observed and predicted mortality for the whole group and also for the subgroups. The study was limited to mortality for reasons mentioned earlier. Others have found satisfactory prediction of morbidity with the POSSUM methodology but for mortality found it necessary to combine this with the P-POSSUM adjustment[10].

The POSSUM scoring system requires collection of simple physiological and operative scores within the scope of basic surgical care. This has obvious advantages over more sophisticated scoring systems such as the Acute Physiology and Chronic Health Evaluation (APACHE) system. The linear comparison analysis using the P-POSSUM equation is straightforward and easy to apply, which is relevant in developing countries with limited resources. This study confirmed that this system is applicable to the Malaysian setting. This validation study opens up ample opportunities for the application of this scoring system as a comparative audit tool to allow assessment of the 'quality' of care[4] in many geographical areas, especially within Commonwealth countries with similar surgical foundations.

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Short note

One visual analogue pain score is sufficient after laparoscopic cholecystectomy

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Introduction

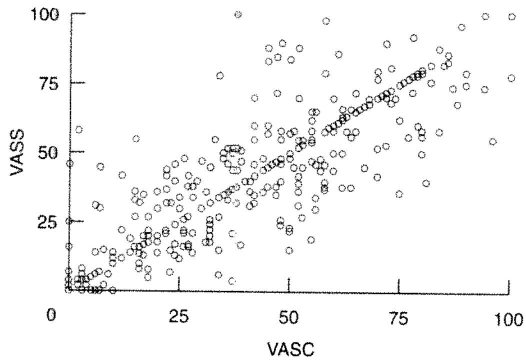
Postoperative pain after abdominal surgery can be assessed with a visual analogue scale (VAS) for pain during rest, while sitting up in bed or while coughing[1,2]. To determine the level of agreement between VAS pain score during coughing or while sitting up, patients who underwent laparoscopic cholecystectomy were investigated.

Patients and methods

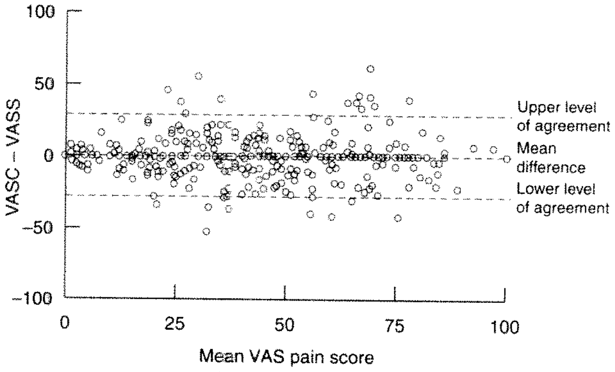
The influence of different sizes of trocar incision was investigated in a prospective randomized trial that included 50 patients who underwent laparoscopic cholecystectomy[3]. The study was approved by the local ethics committee. Informed consent was obtained from each patient. All operations were performed by a similar technique under general anaesthesia with postoperative patient-controlled analgesia. The VAS for pain was explained to all patients before surgery. Pain was rated in a standardized blinded way by the patient on a VAS (where 0 represented no pain and 100 indicated unbearable pain). Pain was scored first during rest, then while lying on the bed and coughing (VASC), and finally when sitting up (VASS) on the evening after surgery and three times per day thereafter. Statistical analysis of all data was performed using SAS 6.12 for Windows95 (SAS Institute, Cary, North Carolina, USA). Postoperative peak scores and area-under-the-curve (AUC) values were calculated. The levels of agreement between VASC and VASS at each time point for each VAS score (VASC, VASS), postoperative peak VAS score (VASC$_{\text{(peak)}}$, VASS$_{\text{(peak)}}$) and AUC values of postoperative VAS scores (VASC$_{\text{(AUC)}}$, VASS$_{\text{(AUC)}}$) were assessed with the technique described by Bland and Altman[4]. The 95 per cent confidence interval (lower and upper level of agreement[4]) and the standard deviation (repeatability coefficient[5]) of the difference between the two measurements were calculated.

Results

Single values for VASC and VASS (*Fig. 1a*), VASC$_{\text{(peak)}}$ and VASS$_{\text{(peak)}}$, and VASC$_{\text{(AUC)}}$ and VASS$_{\text{(AUC)}}$ showed a high correlation with each other (*Table 1*). The level of agreement between single VASC and VASS scores was excellent (*Fig. 1b*, *Table 1*). VASC$_{\text{(peak)}}$ and VASS$_{\text{(peak)}}$, and VASC$_{\text{(AUC)}}$ and VASS$_{\text{(AUC)}}$ also exhibited a very good level of agreement (*Table 1*). The repeatability coefficients of VASC *versus* VASS, VASC$_{\text{(peak)}}$ *versus* VASS$_{\text{(peak)}}$ and VASC$_{\text{(AUC)}}$ *versus* VASS$_{\text{(AUC)}}$ were 13 mm, 17 mm and 1 mm h^{-1} respectively. Therefore, the repeatability coefficients were calculated to be 37 per cent (VASC *versus* VASS), 27 per cent (VASC$_{\text{(peak)}}$ *versus* VASS$_{\text{(peak)}}$) and 26 per cent (VASC$_{\text{(AUC)}}$ *versus* VASS$_{\text{(AUC)}}$) of the mean VAS score.



a Correlation between coughing and sitting pain scores



b Estimated 'true' values

Fig. 1 **a** Correlation between pain scores measured on a visual analogue scale (VAS) while coughing (VASC) and while sitting up (VASS) following laparoscopic cholecystectomy. **b** Estimated 'true' value of VAS score for pain, differences between VAS scores while coughing and while sitting up. Mean difference is shown with upper and lower limit of agreement of VASC and VASS (95 per cent confidence interval)

Table 1 Pearson's correlation and level of agreement between pain scores measured while coughing or sitting up after laparoscopic cholecystectomy

	Mean score	Pearson's correlation		Level of agreement†	
	((VASC + VASS)/2)*	*r*	*P*	Raw data	In % of mean VAS
VAS (mm)	37 (26)	0·86	< 0·001	0 (– 27, 27)	0 (– 73, 73)
$VAS_{(peak)}$ (mm)	62 (21)	0·72	< 0·001	2 (– 31, 35)	3 (– 49, 55)
$VAS_{(AUC)}$ (mm h^{-1})	4 (2)	0·89	< 0·001	0 (– 2, 2)	0 (– 47, 48)

Values are *mean or †mean difference (95 per cent confidence interval). VAS, visual analogue scale; VASC, score measured on VAS while coughing; VASS, score measured on VAS while sitting up; AUC, area under the curve

Discussion

This study evaluated whether the measurement of pain by means of VAS while coughing and while sitting up would yield any additional information in patients who underwent laparoscopic cholecystectomy. The results of this investigation indicate that the level of agreement between the two measurements is high. The considerable variation in the difference between the two VAS scores in this trial confirmed the data collected by DeLoach *et al.*[5], who also found a good agreement between repeated measurements with the VAS score (mean difference 1·52, – 0·83 and – 1·08 mm; repeatability coefficients 17·6, 23·0 and 13·5 mm). Because a decrease in VAS score of less than 8–10 mm on a 100-mm VAS is not registered by patients[6], it can be assumed that after laparoscopic cholecystectomy the mean difference between the two VAS scores does not have any relevant impact. In routine clinical practice and in clinical trials one VAS score, measured either while coughing or while sitting up, is adequate for assessment of postoperative pain after laparoscopic cholecystectomy.

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Original article

Botulinum toxin A in the treatment of patients with Frey syndrome

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Background: This was a prospective study of the treatment of Frey syndrome, also known as gustatory sweating, with botulinum toxin A.

Methods: Thirteen patients with a mean involved skin area of 53 (range 36–80) cm^2, as assessed with the Minor starch–iodine test, were treated with 0·1 ml toxin (75 units/ml) injected intracutaneously into every 4 cm^2 of involved skin. The mean total dose was 100 (range 67·5–150) units. Treatment results were assessed every 3 months with the Minor test. The Frey Questionnaire Card (FQC) was used for subjective assessment. The mean follow-up after primary treatment was 20 (range 9–24) months. Treatment was repeated if the symptoms recurred.

Results: After 3 months 11 of the 13 patients showed a decrease of gustatory sweating of more than 90 per cent. All but one patient with a follow-up of 2 years suffered recurrent gustatory sweating. The mean recurrence-free period after primary treatment was 11 months and that after secondary treatment was 15 months. FQC score and objective assessment correlated well. Treatments were well tolerated, although two patients developed a temporary perioral muscle paresis.

Conclusion: Botulinum toxin A produces good results in the treatment of Frey syndrome. Repeated treatment improves on the results of primary treatment.

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Introduction

After parotidectomy or trauma in the parotid region[1], sweating and flushing of the skin in the cheek, and in the periauricular and temporal region, may occur on the operated side, particularly during meals. Although these symptoms, sometimes referred to as gustatory sweating, were first described by Baillarger[2] in 1853, they are usually referred to as Frey syndrome, described as such by Lucy Frey[3] in 1923.

The reported incidence of Frey syndrome after parotidectomy varies considerably[4], depending on the method of assessment. When objective methods such as the Minor test[5] are used, nearly all patients show signs of Frey syndrome after formal parotidectomy, but only 10–15 per cent have serious complaints[6]. Some authors use questionnaires for the subjective assessment of symptoms[7,8], but there are no reports in the literature on the quantification of these subjective experiences in patients.

The presumed pathophysiological process is the aberrant regeneration of cut parasympathetic fibres between the otic ganglion and the salivary gland tissue[9], leading to innervation of sweat glands and subcutaneous vessels. Gustatory stimulation then results in sweating and redness of the skin in the involved area.

Recently a number of publications on the treatment of Frey syndrome by intracutaneous injection of botulinum toxin have suggested favourable results[6,10–15]. The bacterium *Clostridium botulinum* produces seven toxins, A–G[16]. The toxin that is used for the treatment of Frey syndrome is botulinum toxin A. This neurotoxin enters the cytoplasm of peripheral nerve cells by receptor-mediated endocytosis. On the cytoplasmic side of the cell membrane the toxin breaks down the synaptosome-associated protein SNAP-25 which is essential for the exocytosis of acetylcholine vesicles[17,18]. In this way neurotransmission is blocked until reinnervation occurs by collateral growth of fibres or new SNAP-25 is produced by the cell.

The aim of this study was to analyse botulinum toxin A treatment in patients with serious complaints of Frey syndrome after parotidectomy.

Patients and methods

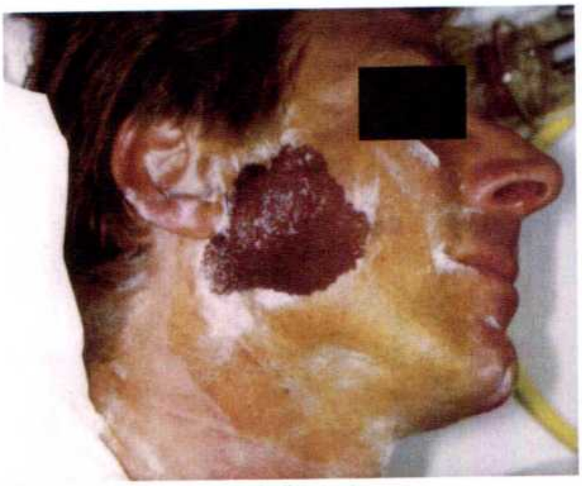
For this study 13 patients were selected who had serious complaints of Frey syndrome after parotidectomy 3–25 years earlier. All patients underwent a formal superficial parotidectomy, 11 for a pleiomorphic adenoma, one for lymphangioma and one because of a cavernous haemangioma. None of the patients underwent radiotherapy. The mean age of the patients was 44 (range 33–65) years and the sex ratio was 1 : 1·2 (M : F).

Objective quantification of the gustatory sweating area was done by the starch–iodine test according to Minor[5]. The affected skin area was covered with iodine solution. After the iodine solution had dried the area was dusted with rice starch powder and the patient was given a lemon sweet. After 5 min the area was coloured deep blue–purple as a result of absorption of the wet iodine by the starch. The coloured area was marked and measured. The area was then divided into 4-cm^2 squares; the middle of each square was marked, indicating the spots where the botulinum toxin should be administered. In all patients photographs were taken (*Fig. 1a* and *1b*).

The medication consisted of Dysport® botulinum toxin type A (Ipsen Farmaceutica, Hoofddorp, The Netherlands). One ampoule of freeze-dried powder containing 500 units toxin in 12·5 ng was dissolved in 6·67 ml 0·9 per cent sodium chloride, resulting in a concentration of 75 units/ml. Some 0·1 ml toxin solution (7·5 units) was injected intracutaneously per 4 cm^2. In this way 67·5–150 (mean 100) units toxin was administered per patient. The treatment was well tolerated by nearly all patients. Only one patient thought the treatment was painful, although bearable.

Follow-up studies were carried out every 3 months. Objective results were checked by the Minor starch–iodine test. A recurrence of gustatory sweating was defined as a colouring of a skin area on the treated side of the face in or near the primary gustatory sweating area larger than 10 per cent of the gustatory sweating area before treatment, irrespective of the intensity of the colouring. New photographs were taken when recurrence was suspected. Follow-up ranged from 6 to 24 months.

Subjective quantification of the symptoms was reported before treatment and at each follow-up visit by a non-validated questionnaire card, the Frey Questionnaire Card (FQC), which was designed for the Frey syndrome after the example of the validated COOP/WONCA card[19]. Patients answered the question 'Did you, for the past 2 weeks, have annoying flushing or perspiration of the cheek during meals?' by indicating one of the following numbers on the card: 1, hardly ever; 2, sometimes but tolerable; 3, regular and unpleasant; 4, often and annoying; 5, always and terribly aggravating.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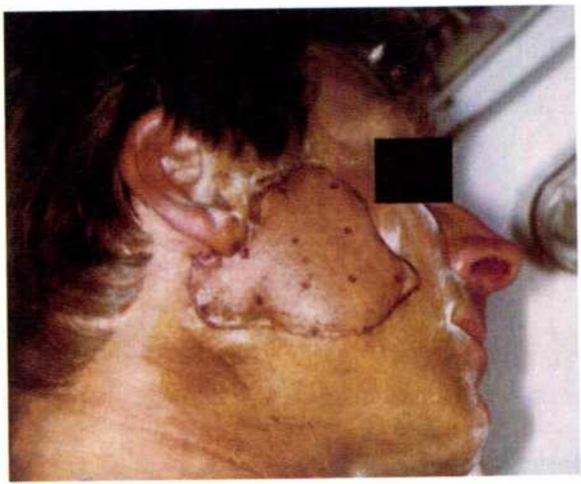
a Positive Minor starch–iodine test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b Marking of injection sites

Fig. 1 **a** Photograph of a patient with Frey syndrome on whom the Minor starch–iodine test has been performed. The gustatory sweating skin has made the wet iodine diffuse into the starch, giving it a blue–purple colour. The dry starch on the unaffected skin has been dusted away. **b** Photograph taken after measurement of the blue starch–iodine area and removal of the wet starch. Each dot of the marker pen indicates the centre of a 4-cm^2 square and marks an intracutaneous injection site

Results

Before treatment the starch–iodine test showed a mean affected skin area of 53 (range 36–80) cm^2. In all but two patients a decrease of more than 90 per cent of the gustatory sweating area was seen after 3 months. One patient was free from recurrent gustatory sweating after 24 months. Two other patients are still free from recurrent sweating, but both have been followed for 9 and 15 months respectively only. The other ten patients suffered recurrent sweating after a mean of 11 (range 3–24) months. In general the sweating area was smaller than before treatment (18 *versus* 53 cm^2) and the intensity of recurrent gustatory sweating was less.

A second treatment with 22·5–82·5 (mean 55) units botulinum toxin was given to patients who showed recurrent gustatory sweating. After the second treatment the first recurrences were seen only after 15 months.

After the first treatment the number of patients without recurrence was 11 at 3 months, 7 at 6 months and 5 at 9 months. Nine patients underwent a second treatment and all were recurrence-free for 9 months. Five of the patients were followed for 15 months and only one recurrence was seen.

The mean FQC score was 4 before treatment, decreasing to 1·8 after 3 months, with a slight increase to 2·3 after 6–9 months. After the second treatment the mean score dropped to 1·4 followed by a slight increase up to 1·9 after 21–24 months. The FQC score indicated a subjective improvement after both treatments as well as a slight subjective decrease at the time of the manifestation of a recurrence.

Two patients developed paresis of the muscles around the corner of the mouth on the injected side during the first week after treatment. In both patients the function of these muscles recovered completely after 10 and 12 weeks. Analysis of the procedure showed that the most anterior injection was probably too close to the corner of the mouth, allowing the botulinum toxin to reach the neuromuscular junctions of the perioral muscles by diffusion. No other complications of treatment were seen. Redness or oedema of the skin did not occur.

Discussion

The chance of developing Frey syndrome after parotidectomy, and the extent to which this occurs, seem to depend on the quantity of parotid tissue that is removed during the operation. Performing a partial superficial parotidectomy rather than a complete superficial parotidectomy, whenever the location and size of the tumour allows this, has reduced the incidence of Frey syndrome by a factor of two[20].

This study demonstrated, in a group of patients suffering from severe symptoms of Frey syndrome, that treatment by means of intracutaneous injection of botulinum toxin A solution at a concentration of 75 units/ml is easy to perform, is associated with little patient discomfort and has good medium-term results, as assessed by the starch–iodine test. The effect of the first treatment lasted for a mean period of 11 months; 8 of 12 patients that were followed for more than 1 year had developed a recurrence 1 year after treatment and 7 of 8 that were followed for 2 years. These results are similar to those reported in literature[6,10–15,21].

There was an impression that the duration of the effect of treatment seemed to depend on the extent of the initial gustatory sweating skin area. Patients with a small affected skin area seemed to have a longer lasting effect of treatment in comparison to patients with an extensive affected skin area; those who had a recurrence within a follow-up period of 9 months had a mean gustatory sweating area of 57 cm^2 and those who had a recurrence after 24 months or no recurrence at that time had a mean area of 45 cm^2. However, Laccourreye *et al.*[12], who specifically looked at a possible correlation between the duration of the effectiveness of intracutaneous injection of botulinum toxin A and the involved skin surface, did not find a statistically significant relationship.

Although most patients developed recurrent gustatory sweating, the affected area was always smaller than that before treatment (18 *versus* 53 cm^2). The quantity of sweat produced per unit area in the region of recurrence seemed smaller than that before treatment. However, the starch–iodine test provides no means of determining the exact quantity of sweat that is produced. A blotting paper test[22] might be helpful in this regard.

If recurrence occurs the treatment can be repeated with a good response, and without any complications. Other studies have also reported on reinjection after recurrent gustatory sweating without complications[12,14]. In this study the duration of the effect of such a consecutive treatment exceeded that of the first treatment by at least 5 months. The effect of a third or further treatment is unknown but one would expect that the regenerative capacity of the parasympathetic nerves is limited and that degeneration and atrophy of these nerves might occur after several treatments.

Comparison of results scored with the FQC and the outcome of the starch–iodine tests showed that patients with a lower FQC score (2 or 3) had a longer recurrence-free interval after treatment than patients with a higher FQC score (4 or 5): 15 *versus* 7–8 months respectively. A raised FQC score after the initial lowering of the score as result of treatment was seen around the time of recurrence. Thus the FQC seems a useful instrument with which to assess patients before treatment and during follow-up.

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Corrigendum

A corrigendum is a published correction made by authors to alert readers to a serious error in a paper. *BJS* has been advised by the authors of 'Randomized double-blind controlled trial of roxithromycin for prevention of abdominal aortic aneurysm expansion' (*Br J Surg* 2001; **88:** 1066–72) of just such an error.

In this paper some of the expansion rates expressed in *Table 2* are erroneous; this has led to further errors in column four of *Table 3*. It is also noted that the confidence intervals in column two of *Table 3* should be negative. The correct versions of the tables are published below, along with an appropriately altered abstract. The authors changes are highlighted below in bold text. Readers should also note that the first sentence under 'Aneurysm expansion' on page 1070 should be deleted.

The authors state that the errors in their original paper have not influenced the conclusions of their article and they apologise to readers for any confusion caused.

Table 2 Mean annual expansion for abdominal aortic aneurysms in the intervention and placebo groups during follow-up

	First year			Second year			Overall observation period			
	Macrolide	Placebo	*P*†	Macrolide	Placebo	*P*†	Macrolide	Placebo	*P*†	OR‡
Expansion rate (mm per annum)										
All AAAs	1·56	2·80	0·02	2·06	2·16	0·64	**1·97**	**2·72**	**0·24**	
AAA <36·5 mm	1·34	2·34	0·16	2·08	0·45	0·17	**1·70**	**2·07**	**0·55**	
AAA ≥36·5 mm	1·76	3·31	0·08	2·03	3·19	0·53	**2·22**	**3·44**	**0·23**	
IgA titre <20 EIU	1·64	2·52	0·08	1·80	1·13	0·31	**1·99**	**2·34**	**0·49**	
IgA titre ≥20 EIU	1·12	3·84	0·19	2·57	3·49	0·77	**1·87**	**4·11**	**0·14**	
No. of patients										
Size ≥36·5 mm	23	20		23	27		24	24		2·33 (0·46–15·43)
IgA titre ≥20	8	9		—	—		14	18		0·78 (0·24–2·49)
Expansion rate >2 mm per year	14	22		6	11		14	23		0·37 (0·11–1·29)
Referred for surgery*	4	3		1	4		5	7		0·79 (0·18–3·18)
Acute myocardial infarction	0	1		0	3		0	4		—
Lost to follow-up	2	3		3	1		5	4		1·48 (0·29–7·98)
Dead	2	1		1	1		3	2		1·76 (0·19–21·95)

*due to demanding size of the AAA. Ig, immunoglobulin; EIU, enzyme immunounits. †Student's *t* test, Fisher's exact test; ‡Odds ratio (OR) with 95 per cent confidence interval in parentheses

Table 3 Roxithromycin treatment and predictors of expansion for small aneurysms using linear regression analysis

	Expansion rate (mm per annum)		
	First year	Second year	Whole study interval
AAA size, mm	0·16 (0·04 to 0·27)	0·23 (0·05 to 0·42)	**0·20 (0·09 to 0·31)**
Roxithromycin	– 1·91 (– 3·18 to **– 0·65)**	– 0·43 (– 2·31 to 1·45)	**– 1·53 (– 2·70 to – 0·40)**
Diastolic blood pressure, mmHg	– 0·02 (– 0·07 to 0·03)	– 0·06 (– 0·13 to 0·01)	– 0·02 (– 0·07 to 0·03)
IgA antibodies, all levels	0·02 (– 0·02 to 0·05)	0·00 (– 0·51 to 0·05)	0·01 (– 0·02 to 0·05)
Smoker*	0·87 (– 0·44 to 2·19)	1·68 (– 0·41 to 3·77)	**0·82 (– 0·40 to 2·03)**
Median AAA < 36·5 mm	0·32 (– 0·07 to 0·70)	0·01 (– 0·81 to 0·83)	**0·19 (– 0·19 to 0·56)**
Roxithromycin	– 1·57 (– 3·12 to **– 0·02)**	1·07 (– 2·28 to 1·58)	**– 0·40 (– 1·89 to 1·09)**
Diastolic blood pressure, mmHg	– 0·05 (– 0·11 to 0·01)	0·00 (– 0·81 to 0·83)	**– 0·03 (– 0·08 to 0·03)**
IgA antibodies, all levels	0·07 (– 0·11 to 0·12)	– 1·46 (– 1·23 to 0·10)	**0·03 (– 0·02 to 0·08)**
Smoker*	0·35 (– 1·63 to 2·34)	2·15 (– 2·15 to 6·45)	**0·92 (– 0·98 to 2·83)**
Median AAA ≥ 36·5 mm	0·34 (0·10 to 0·57)	0·37 (– 0·17 to 0·90)	**0·33 (0·08 to 0·59)**
Roxithromycin	– 2·64 (– 4·41 to **– 0·92)**	– 0·99 (– 4·31 to 2·35)	**– 2·47 (– 4·34 to – 0·60)**
Diastolic blood pressure, mmHg	– 0·02 (– 0·08 to 0·04)	– 0·01 (– 0·23 to 0·03)	**– 0·03 (– 0·10 to 0·04)**
IgA antibodies, all levels	0·00 (– 0·05 to 0·04)	0·00 (– 0·08 to 0·03)	**0·01 (– 0·04 to 0·06)**
Smoker*	0·68 (– 1·03 to 2·40)	2·49 (– 1·38 to 6·36)	**0·95 (– 0·91 to 2·82)**
Initial IgA level ≥ 20 EIU (*n* = 17)	0·00 (– 0·11 to 0·11)	– 0·02 (– 0·10 to 0·06)	**– 0·03 (– 0·12 to 0·06)**
AAA size, mm	– 0·18 (– 0·84 to 0·49)	0·00 (– 0·37 to 0·78)	**0·01 (– 0·52 to 0·55)**
Roxithromycin	– 0·31 (– 4·30 to 3·68)	0·22 (– 4·43 to 2·48)	**0·34 (– 2·87 to 3·55)**
Diastolic blood pressure, mmHg	– 0·10 (– 0·24 to 0·04)	– 0·09 (– 0·19 to 0·02)	**– 0·09 (– 0·12 to 0·06)**
Smoker*	0·02 (– 5·90 to 5·87)	0·17 (– 4·51 to 4·99)	**0·19 (– 4·54 to 4·93)**

Values in parentheses are 95 per cent confidence intervals. *Yes = 1, no = 0. AAA, abdominal aortic aneurysm; Ig, immunoglobulin, EIU, enzyme immunounits

Background: Macrolide treatment has been reported to lower the risk of recurrent ischaemic heart disease. The influence of macrolides on the expansion rate of abdominal aortic aneurysms (AAAs) remains unknown. The aim was to investigate the effect of roxithromycin on the expansion rate of small AAAs.

Methods: A total of 92 subjects with a small AAA were recruited from two populations. One population consisted of 6339 men aged 65–73 years who were offered a hospital-based mass screening programme for AAA. From this population 66 subjects were recruited. The remaining 26 men were recruited from among 49 subjects diagnosed at interval screening for an initial aortic diameter between 25 and 29 mm. Subjects were randomized to receive either oral roxithromycin 300 mg once daily for 28 days or matching placebo, and followed for a mean of 1·5 years.

Results: During the first year the mean annual expansion rate of AAAs was reduced by **44** per cent in the intervention group (1·56 mm per year), compared with 2·80 mm per year following placebo (*P* = 0·02). **During the second year the difference was only 5 per cent.** Multiple linear regression analysis showed that roxithromycin treatment and initial AAA size were significantly related to AAA expansion when adjusted for smoking, diastolic blood pressure and immunoglobulin A level of 20 or more. Logistic regression analysis confirmed a significant difference in expansion rates above 2 mm annually between the intervention and placebo groups: odds ratio = 0·09 (95 per cent confidence interval 0·01–0·83).

Conclusion: In comparison to placebo, roxithromycin 300 mg daily for 4 weeks reduced the expansion rate of AAAs.

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Responses can be sent electronically via the BJS *website (www.bjs.co.uk) or by post. All letters will be reviewed and, if approved, appear on the website. A selection of these will be edited and published in the Journal. Letters must be no more than 250 words in length. Letters submitted by post should be typed on A4-sized paper in double spacing and should be accompanied by a disk.*

Prospective randomized multicentre trial comparing stapled with open haemorrhoidectomy (*Br J Surg* 2001; 88: 669–74)

Sir

The authors should be commended for reporting relatively long-term results for this new procedure. Unfortunately some of the conclusions are somewhat misleading. They state that 'stapled haemorrhoidectomy has at least the same effectiveness as the conventional Milligan–Morgan procedure', but the results show a recurrent haemorrhoidal prolapse rate of 20 per cent after stapled haemorrhoidectomy compared with 6 per cent after Milligan–Morgan haemorrhoidectomy and a persistence of 12 per cent of external piles after stapled haemorrhoidectomy compared with only 1 per cent following Milligan–Morgan haemorrhoidectomy. Stapled haemorrhoidectomy carries less postoperative pain and allows earlier return to work[1–3], but further studies are needed to confirm its effectiveness in the long term by evaluating recurrence rate and the treatment of external piles. The group should be encouraged to follow the patients in this trial and report the long-term results of the whole series.

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3 Seow-Choen F. Stapled haemorrhoidectomy: pain or gain. *Br J Surg* 2001; **88:** 1–3.

Author's reply

Sir

I disagree with Dr Pescatori's comment regarding prolapse recurrence. In fact the reported episodes of prolapse of 21 *versus* 7 per cent (and not 1 per cent) are referring to the first postoperative month. In the long-term follow-up there were six patients (12 per cent) in the stapled group and one in the Milligan–Morgan group (*P* not significant) complaining of residual skin fibrous folds which were not residual haemorrhoids. These patients are being reviewed every 6 months and long-term results will be presented in the future.

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Provision of long-term vascular access for haemodialysis in a patient with exhausted superficial arm veins (*Br J Surg* 2001; 88: 484–5)

Sir

We agree that one must try veins before opting for a prosthetic graft for patients with failed primary and secondary vascular access (*Table 1*). The basilic vein 'hidden' from venipuncture, an anatomical blessing in disguise, has provided a reliable option.

Table 1 Impact of brachio-basilic vein transposition on the need for polytetrafluoroethylene graft arteriovenous fistula

Period	January 1993 – December 1996	January 1997 – September 2001
Brachio-basilic vein transposition	13	55
Polytetrafluoroethylene graft fistula	118	73

$P < 0{\cdot}001$, χ^2 test

Both this article and Murphy *et al.*[1] describe how the mobilized, disconnected, arterialized basilic vein is transposed into a relatively lateral tunnel and then re-anastomosed to the brachial artery (apparently a one-stage procedure). A two-stage transposition has become standard in our unit[2]. This offers the possibility of avoiding the second stage (of tunnelling and re-anastomosis) in a patient who develops venous hypertension or arterial 'steal' after the first stage.

With experience we noted that the dissection of the brachial artery at the second stage in a previously operated area was rather tedious. This led us to choose either superficialization or to anastomose the mobilized, disconnected, arterialized basilic vein to the brachial artery more proximally. Further modification has greatly simplified the procedure without compromising the extent of lateralization: re-anastomosis of the tunnelled mobilized, disconnected, arterialized basilic vein to the arterial end of stump of the mobilized, disconnected, arterialized basilic vein, thereby avoiding dissection of the artery in the second stage, about 4 cm proximal to cubital fossa crease.

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1 Murphy GJ, White SA, Knight AJ, Doughman T, Nicholson ML. Long-term results of arteriovenous fistulas using transposed autologous basilic vein. *Br J Surg* 2000; **87**: 819–23.
2 Kumar A, Sinha S, Sharma AK. Long-term results of arteriovenous fistulas using transposed autologous basilic vein. *Br J Surg* 2000, **87**: 1735–6 (letter).

Chronic pain and quality of life following open inguinal hernia repair (*Br J Surg* 2001; 88: 1122–6)

Sir

This report and another[1] have called attention to a remarkable and unacceptably high incidence of chronic pain following repair of inguinal hernia. It seems unlikely that such symptoms would go unnoticed prior to 1990, although good studies of this problem prior to that are not available. If the incidence of chronic pain is as high as recently reported, it is incumbent on the surgical community to address the causes and institute preventive measures. I should like to propose one mechanism for prevention of the pain based on my experience of observing that many of these patients experience marked pain when coughing or sneezing, or after prolonged standing. These symptoms can be and have been completely obviated by my removal of unyielding stiff polypropylene or nylon sutures, or stiff mesh which have only come into frequent use during the last 10 years. The instantaneous relief is impressive indeed. It is lamentable that large studies on this subject do not detail the suture technique employed for the repair.

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1 Cunningham J, Temple WJ, Mitchell P, Nixon JA, Preshaw RM, Hagen NA. Cooperative hernia study: pain in the postrepair patient. *Ann Surg* 1996; **224**: 598–602.

One thousand consecutive gastrectomies without operative mortality

Sir

Recently we privately celebrated the discharge of a patient who underwent gastrectomy for early gastric cancer. She was the 1000th patient to undergo gastrectomy in our Division since a patient had died of a postoperative complication in 1998. We are proud that, during these 2·5 years, all 1000 patients survived the operation and were discharged. Several British surgeons have visited the Division and witnessed our management of gastric cancer[1–3].

We perform on average nine gastrectomies a week; the four staff surgeons, who have an experience of more than 500 gastrectomies each, participating in 99 per cent of the operations. D2 gastrectomy is always the standard and some patients undergo a more extended operation for locally advanced carcinoma. In the 1000 patient series pancreatic fistula developed in 15 per cent of cases following total gastrectomy with splenectomy, and reoperation was sometimes necessary for bleeding or abscess formation. Management of complications, however, has improved and been standardized as a result of careful evaluation of past cases. In addition, a recent change of reconstruction method from Billroth I to Roux-en-Y after distal gastrectomy, together with the improved stapling technique after total gastrectomy, have reduced the anastomotic leak rate to almost zero[4].

We believe that the zero mortality is a monument to technical specialization. Radical D2 gastrectomy may be associated with high operative mortality, 13 per cent in some situations[5], especially during the learning curve. This is a problem which may be overcome with specialization of cancer management, particularly in the field of surgical oncology.

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1 Hardwick R. Fellowships: visit to National Cancer Center Tokyo. *Ann R Coll Surg Engl* 1999; **81**: 282–5.
2 Gupta R. Lessons in treatment of gastric cancer: viewpoint of a UK surgeon. *Jpn J Clin Oncol* 2000, **30**: 369–70.
3 Davis PA. The management of patients with gastric cancer. can west meet east? *Jpn J Clin Oncol* 2000; **30**: 463–4.
4 Nomura S, Sasako M, Katai H, Sano T, Maruyama K Decreasing complication rates with stapled esophagojejunostomy following a learning curve. *Gastric Cancer* 2000; **3**: 97–101.
5 Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V *et al* Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. *Lancet* 1996; **347**: 995–9.

Handbook of Patient Care in Vascular Diseases (4th Ed.)

J. W. Hallett Jr, D. C. Brewster and T. E. Rasmussen

220 × 108 mm. Pp. 317. Illustrated. 2001. Philadelphia, Pennsylvania: Lippincott, Williams & Wilkins. $39·95.

To compete for essential space with a bleep, stethoscope and diary, a handbook has to be logical and structured with all the basics easily accessible with recent key references. To assess its everyday practical value, the book was also reviewed by a vascular surgical trainee (Y. C. Chan). It begins with concise pathophysiology and excellent advice on clinical examination for the undergraduate or doctor beginning his or her career. In Chapter 2 we looked for a section on the investigation of haematological or biochemical risk factors in 'initial patient evaluation' but, apart from optimizing the management of the diabetic patient and giving global weight reduction advice, American Society of Anesthesiologists grading is reached without much being included about smoking cessation or risk factor evaluation. We eventually discovered the preoperative management of coagulation disorders in Chapter 25, right at the end of the book. Another criticism is that the role of the vascular laboratory is discussed with undue emphasis on the slightly dated use of plethysmographic techniques and, in particular, pulse volume recording. The value of quality training of staff in the use of hand-held Doppler instruments and the extent of information obtained needs expansion. Colour duplex scanning is covered but the text lacks depth on more recent advances, such as power Doppler. The ability of duplex scanning to image vessels as an alternative to conventional angiography and to provide velocity measurements across stenoses is understated. This book has evidence-based chapters on percutaneous transluminal angioplasty, stenting and thrombolysis, but there is no specific mention of the risks of cerebral haemorrhage in the elderly. It fills a gap in the pocket but perhaps not in the market.

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Errors, Medicine and the Law

A. Merry and A. McCall Smith

227 × 151 mm. Pp. 254. Illustrated. 2001. Cambridge: Cambridge University Press. £47·50.

There can be little doubt that the public appreciation of modern healthcare includes the perception of an epidemic of iatrogenic harm. Some adverse clinical incidents are the result of professional negligence on the part of surgeons, but more often they are the inevitable concomitants of the complexity of modern healthcare. This book is about distinguishing the former from the latter.

In these medicolegally troubled times it is not surprising that several books on negligence have recently been published for doctors; these works generally deal with practical matters such as methods of reducing risk, life as a defendant and as an expert witness, and how complaints are handled at various levels, including the courts. The present volume is in many ways complementary to such 'nuts and bolts' books, providing a rather more intellectual discourse on accidents and blame than is usual. It is written in exemplary English by a cardiac anaesthetist (A. Merry) and a professor of medical law (A. McCall Smith), and must surely be of interest to anyone practising at the 'sharp end' of medicine. Having read *Errors, Medicine and the Law* may not keep you afloat on the sea of blame, but at least you will realize just how far away landfall really is.

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Upper Gastrointestinal Surgery (2nd Ed.)

S. M. Griffin and S. Raimes (eds)

252 × 198 mm. Pp. 474. Illustrated. 2001. London: WB Saunders. £54·95.

The editors of this book deserve unreserved congratulations. Each contributor has produced a concise chapter with a maximum of evidence-based argument and a minimum of opinion. My bible was Glynn Jamieson's *Oesophagus* – a great work, full of detail and leading opinion, and still most useful. However times have changed and there is now much more evidence-based guidance (not all of it necessarily watertight) than there was in the 1980s, allowing a much more confident statement of what is best practice.

My first reaction to this second edition was one of real pleasure, even excitement, at a style which draws one through each chapter. The 'scalpel codes', with their eye-catching format, highlight data that are 'beyond reasonable doubt' and provide incentive to keep reading.

The surgical authors are all familiar names with a known bias to evidence-based writing, and their opinions reflect contemporary best practice. Examples are the superb handling of Barrett's metaplasia by Barr and the even handed evaluation of antireflux surgery by Watson and Jamieson. The ancillary chapters on pathology, anaesthesia, postoperative care and radiochemotherapy are excellent and we are spared the tedium of each specialty's chestnuts.

This book provides an attractive, authoritative, up-to-date account of upper gastrointestinal surgery in the UK at the beginning of the third millennium. I recommend it unreservedly to trainees and consultants; it is cheap enough to buy without thinking too hard about it.

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Current Therapy in Vascular Surgery (4th Ed.)

C. B. Ernst and J. C. Stanley (eds)

284 × 220 mm Pp 944 Illustrated 2001 St Louis, Missouri Mosby
£125 00

No less than 328 contributors, all but two or three from the USA, have written sections for the latest edition of this major textbook under the editorial control of Calvin Ernst and James Stanley. The names of many authors will be familiar to British vascular surgeons while others are less well known. The format of the book is one that I find attractive and useful, consisting of numerous brief chapters, most no more than three or four pages long, each devoted to a specific clinical condition or problem. They are grouped together under the expected general headings (cerebrovascular disease, upper extremity arterial disease, aortic aneurysm, etc.) and I found it both easy to locate a chapter on a particular problem and tempting to browse through others at random. The wide range of topics covers virtually every aspect of arterial, venous and lymphatic disease, from the routine (e.g. surgical management of non-ruptured infrarenal aortic aneurysm) to the frankly obscure (e.g. persistent sciatic artery).

It is not a textbook of operative technique, although many surgical procedures are described in some detail and illustrated with, in general, good quality black and white diagrams or radiographs. Unsurprisingly, with so many authors, chapter quality is variable. The best provide a clear and concise overview of their dedicated topic while a few might be criticized for a rather didactic approach. Preparation of a book of this sort is a slow process and this is proved by the fact that very few references are later than 1998. In the majority of cases this does not detract from the value of the contribution, although chapters dealing with rapidly evolving topics, such as endovascular aneurysm repair, already seem a little dated.

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Colour Atlas of Surgery

R. Lall Gupta and R. K. Agarwal

288 × 225 mm Pp 207 Illustrated 2000 New Delhi Jaypee Brothers

From infections and infestations through to congenital malformations, each of the 24 chapters in this atlas is devoted to a different organ system or topic so that in total they cover the gamut of surgical diseases. Each chapter has a consistent format containing good quality photographs illustrating the various conditions, most of which are in colour and pithily captioned. One of the strengths of this atlas, hailing as it does from India, is that many of the diseases are shown at an advanced stage of presentation, making it easy to pick out the pertinent physical signs. This is particularly true of the sections dealing with diseases of the head and neck. Included within each chapter are descriptions of the pathologies, though most are too short to act as anything more than *aides-mémoire*. Read in conjunction with a standard surgical text, however, this book will prove an informative and at times fascinating companion that should appeal to medical and membership students alike.

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Scientific Surgery

The *BJS* is committed to the practice of surgery based on scientific evidence. Each month we will publish a list of randomized trials and meta-analyses collated from English-language publications. A collection of all these papers will be available in the Scientific Surgery archive which will be held on the *BJS* website together with links to free Medline sites where the full papers can be accessed (see below for details). If you have recently published a randomized trial that has not been featured in Scientific Surgery, the Editors would be pleased to receive a reprint and consider its inclusion.

Lewis SJ, Egger M, Sylvester PA, Thomas S. Early enteral feeding *versus* 'nil by mouth' after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. *BMJ* 2001; **323:** 773–6.

Eleven studies including 837 patients were analysed. Early enteral nutrition significantly reduced postoperative infection (relative risk 0·72) and duration of hospital stay. There were non-significant reductions in other complications and mortality.

Wasvary HJ, Hain J, Mosed-Vogel M, Bendick P, Barkel DC, Klein SN. Randomized, prospective, double-blind, placebo-controlled trial of nitroglycerin ointment on pain after haemorrhoidectomy. *Dis Colon Rectum* 2001; **44:** 1069–73.

In this study of 39 operations, nitroglycerin ointment reduced the need for postoperative morphine but half the patients developed a significant headache and required more oral analgesia.

Jonas M, Neal KR, Abercrombie JF, Scholefield JH. A randomized trial of oral *versus* topical diltiazem for chronic anal fissures. *Dis Colon Rectum* 2001; **44:** 1074–8.

Topical treatment healed more fissures after 8 weeks (65 *versus* 38 per cent, $P = 0.001$), with fewer side-effects in a study of 50 patients.

Carli F, Trudel JL, Belliveau P. The effect of intraoperative thoracic epidural anesthesia and postoperative analgesia on bowel function after colorectal surgery: a prospective, randomized trial. *Dis Colon Rectum* 2001; **44:** 1083–9.

Epidural analgesia was compared with patient-controlled morphine after 42 operations. Pain scores and median time to first flatus were reduced with epidural analgesia, but complication rates and duration of hospital stay were similar.

Nguyen NT, Goldman C, Rosenquist CJ, Arango A, Cole CJ, Lee SJ *et al.* Laparoscopic *versus* open gastric bypass: a randomized study of outcomes, quality of life and costs. *Ann Surg* 2001; **234:** 279–91.

The study included 155 patients. Laparoscopic banding took longer but significantly reduced hospital stay, wound complications and quality of life at 6 months. Weight loss was similar after 1 year.

Oostenbrink JB, Tangelder MJD, Busschbach JJV, van Hout BA, Buskens E, Algra A *et al.* Cost-effectiveness of oral anticoagulants *versus* aspirin in patients after infrainguinal bypass grafting surgery. *J Vasc Surg* 2001; **34:** 254–62.

Further results from this multicentre study of 2650 patients. Healthcare costs, event-free survival and quality-adjusted life years were similar.

Laine T, Aarnio P. How often does glove perforation occur in surgery? Comparison between single gloves and a double-gloving system. *Am J Surg* 2001; **181:** 564–6.

Some 2462 gloves were tested; the perforation rate was 8 per cent. The clinical detection rate was greater in the new double-glove system than routine single gloving (86 *versus* 37 per cent). The inner glove was perforated in only 7 per cent of outer glove perforations.

Ferraz AAB, Wanderley GJP, Santos Jr MA, Mathias CA, Araujo Jr JGC, Ferraz EM. Effects of propranolol on human postoperative ileus. *Dig Surg* 2001; **18:** 305–10.

This study was conducted in patients with schistosomiasis undergoing surgery. Myoelectric activity in bipolar electrodes in the left colon was not affected by preoperative treatment with propranolol.

Kapiteijn E, Marijnen CAM, Nagtegaal ID, Putter H, Steup WH, Wiggers T *et al.* Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; **345:** 638–46.

The trial included 1861 patients. After 2 years, local recurrence was reduced by the addition of radiotherapy (2·4 *versus* 8·2 per cent, $P < 0.001$), but survival rates were similar (82·0 *versus* 81·8 per cent respectively).

Rose JS, Levitt MA, Porter J, Hutson A, Greenholtz J, Nobay F *et al.* Does the presence of ultrasound really affect computed tomographic scan use? A prospective randomized trial of ultrasound in trauma. *J Trauma* 2001; **51:** 545–50.

In patients with multiple blunt injuries, routine ultrasonography reduced the need for subsequent computed tomography to 37 of 104 patients compared to 54 of 104 controls ($P < 0.01$).

The *BJS* website can be found at *http://www.bjs.co.uk*. In addition to details of current and previous articles featured in Scientific Surgery, the website contains details of the Editorial Team and Board, instructions to prospective authors, links to other sites (such as The Cochrane Library) and forthcoming surgical events. The Editors welcome comments and suggestions about the website, either in writing or through the website address.

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Original articles should normally be in the format of introduction, patients and methods, results and discussion. Please provide a 200-word structured abstract. Lengthy manuscripts will be returned for shortening. The discussion in particular should be clear and concise and limited to matters arising directly from the results. Avoid discursive speculation. **Randomized clinical trials** should be clearly identified as such in the title and abstract.

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The Editorial Board of the *BJS* encourages submission of review articles or meta-analyses on topics of interest. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted article will receive an honorarium. Before submission of a meta-analysis of randomized trials, authors are encouraged to consult the QUORUM statement, designed to assist in improving the quality of the submission (*Lancet* 1999; 354: 1896–900). Potential authors are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

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The Editors commission leading articles that are 600–900 words in length and address controversial topics of current interest. They should be supported by no more than ten key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

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The Editors welcome topical correspondence from readers relating to articles published in the Journal. Responses can be sent

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Manuscripts must be clearly reproduced with adequate space for editorial notes. Present the text on one side of sheets of A4 paper (210 × 297 mm) with double spacing and 4-cm margins. **Begin each section (abstract, introduction, patients and methods, results and discussion) on a new page. Manuscripts that do not conform to these requirements will be returned for recasting.**

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On the title page give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) **the name, postal and email addresses, telephone and facsimile numbers of the author responsible for correspondence and to whom requests for reprints should be addressed;** (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, review, etc).

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This must not exceed 200 words and should be presented in a structured format. **Background**: state why the study was done and its main aim. **Method**: describe patients, laboratory material and other methods used. Clearly identify the nature of the study, i.e. randomized controlled trial, retrospective review, experimental study, etc. **Results**: state the main findings including important numerical values. **Conclusion**: state the main conclusions but controversial or unexpected observations may be highlighted.

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Submit four copies of all illustrations and tables. Type each table on a separate page with a brief title. Line drawings are acceptable as clear black on white graphics, computer print-out or photocopies. Submit radiographs, photomicrographs, etc unmounted in the form of glossy prints, original transparencies or negatives. Illustrations in colour are encouraged and will be printed at no cost to the author. If you include photocopies, they should be of sufficient quality to enable the Journal's referees to judge their content and value. Label each illustration on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); indicate the top of the illustration. Include a measure of magnification of photomicrographs. Include explanations of symbols and shading within the figure. Survival curves must be accompanied by a table giving the actual numbers of patients involved. Include in the legends to illustrations and the footnotes to tables brief but comprehensive explanations of all the information presented. Look at recent issues of the Journal for examples of accepted layout. Any table or illustration reproduced from a published work must give the original source in full. You must obtain permission from the original author and the publisher before submission.

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Use abbreviations *sparingly*. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension. Abbreviations must be used consistently and must be defined on first use.

Numbers and units

Use the decimal point, not a comma, for example 5·7. Use a space and not a comma after thousands and multiples thereof, for example 10 000. Use SI units (International System of Units) except for the measurement of blood pressure (mmHg).

Statistics

For detailed guidance on the handling of statistical material consult *Br J Surg* 1991; **78**: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, the chosen end-points and justify the sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (www.consort-statement.org).

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Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished and presented in parentheses after the mean values.

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Clearly describe methods used for each analysis. Methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value. Actual *P* values should be reported to three decimal places, especially when the result is not significant. The results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

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Type the references with double spacing in the Vancouver style (see **Preparation of manuscripts**). Reference to abstracts and personal communications is discouraged. Reference to unpublished communications will not be accepted.

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Contents of Volume 88

Number 1

Leading article

Stapled haemorrhoidectomy: pain or gain 1
F. Seow-Choen

Reviews

Systematic review of antimicrobial agents for chronic wounds 4
S. M. O'Meara, N. A. Cullum, M. Majid and T. A. Sheldon

Experimental models of Gram-negative sepsis 22
S. J. Parker and P. E. Watkins

Somatostatin receptor imaging, therapy and new strategies in patients with neuroendocrine tumours 31
G. D. Slooter, A. Mearadji, W. A. P. Breeman, R. L. Marquet, M. de Jong, E. P. Krenning and C. H. J. van Eijck

Randomized clinical trials

Randomized clinical trial of diathermy *versus* scalpel incision in elective midline laparotomy 41
S. R. Kearns, E. M. Connolly, S. McNally, D. A. McNamara and J. Deasy

Randomized trial of needlescopic *versus* laparoscopic cholecystectomy 45
W. K. Cheah, J. E. Lenzi, J. B. Y. So, C. K. Kum and P. M. Y. Goh

Original articles

Incidence of benign lesions in patients resected for suspicious hilar obstruction 48
M. F. Gerhards, P. Vos, T. M. van Gulik, E. A. J. Rauws, A. Bosma and D. J. Gouma

The National Liver Transplantation Audit: an overview of patients presenting for liver transplantation from 1994 to 1998 52
P. Hartley, A. Petruckevitch, B. Reeves and K. Rolles on behalf of the steering group of the UK Liver Transplantation Audit

Experimental study of type 3 phosphodiesterase inhibitor on liver graft function 59
T. Ikegami, T. Nishizaki, S. Hiroshige, R. Ohta, K. Yanaga and K. Sugimachi

Potential of laparoscopic ultrasonography as an alternative to operative cholangiography in the detection of bile duct stones 65
S. E. Tranter and M. H. Thompson

Use of cadaveric superior mesenteric artery as interpositional vascular graft in orthotopic liver transplantation 70
P. Muiesan, M. Rela and N. D. Heaton

Postoperative liver function after elective right hepatectomy in elderly patients 73
G. M. Ettorre, D. Sommacale, O. Farges, A. Sauvanet, O. Guevara and J. Belghiti

Suitability for endovascular aneurysm repair in an unselected population 77
K. R. Woodburn, H. Chant, J. N. Davies, K. S. Blanshard and S. J. Travis

Training in infrainguinal bypass surgery for severe leg ischaemia 82
L. Papp, S. M. Evans, J. Kelman, R. T. A. Chalmers, J. A. Murie and A. W. Bradbury

Experimental sodium phosphate and polyethylene glycol induce colonic tissue damage and oxidative stress 85
A. Coskun, A. Uzunkoy, S. A. Duzgun, M. Bozer, I. Ozardali and H. Vural

Insulin-like growth factor I and truncated keratinocyte growth factor accelerate healing of left-sided colonic anastomoses 90
B. Egger, R. Inglin, J. Zeeb, O. Dirsch, Y. Huang and M. W. Buchler

Blinded prospective study of the incidence of deep venous thrombosis following conventional or laparoscopic colorectal resection (short note) 99
J. W. Mall, W. Schwenk, O. Rodiger, K. Zippel, C. Pollmann and J. M. Muller

Value and cost of follow-up after adjuvant treatment of patients with Dukes' C colonic cancer 101
W. A. Bleeker, N. H. Mulder, J. Hermans, R. Otter and J. T. M. Plukker

High-risk colorectal adenomas and serum insulin-like growth factors 107
A. G. Renehan, J. E. Painter, W. S. Atkin, C. S. Potten, S. M. Shalet and S. T. O'Dwyer

Prospective evaluation of the morbidity of axillary clearance for breast cancer 114
M. Duff, A. D. K. Hill, G. McGreal, S. Walsh, E. W. McDermott and N. J. O'Higgins

Detection, treatment and outcome of axillary recurrence after axillary clearance for invasive breast cancer 118
R. de Boer, H. F. P. Hillen, R. M. H. Roumen, H. J. T. Rutten, M. J. C. van der Sangen and A. C. Voogd

Impact of mammographic interval on stage and survival after the diagnosis of contralateral breast cancer 123
R. Kaas, A. A. M. Hart, A. P. E. Besnard, J. L. Peterse and E. J. T. Rutgers

Laparoscopically assisted total or distal gastrectomy with lymph node dissection for early gastric cancer 128
T. Asao, Y. Hosouchi, T. Nakabayashi, N. Haga, E. Mochiki and H. Kuwano

Selection of patients for laparoscopic repair of perforated peptic ulcer 133
F. Y. J. Lee, K. L. Leung, P. B. S. Lai and J. W. Y. Lau

Analysis of local recurrence and optimizing excision margins for cutaneous melanoma 137
A. K. T. Ng, W. O. Jones and J. H. F. Shaw

The intestinal flora influences adhesion formation around surgical anastomoses 143
C. Bothin, M. Okada, T. Midtvedt and L. Perbeck

Double near and far Prolene suture closure: a technique for abdominal wall closure after laparostomy (short note) 146
R. A-Malik and N. A. Scott

Response of visceral peritoneum to abdominal surgery 148
M.-L. Ivarsson, P. Falk and L. Holmdahl

Correspondence 152

Book reviews 157

Scientific surgery 158

Instructions to authors 159

Number 2

Leading article

Probiotics 161
G. C. O'Sullivan

Clinical dilemma

Rectal adenocarcinoma with liver metastases: management of the primary tumour 163
A. Sarela and D. S. O'Riordain

Reviews

Portal vein embolization: rationale, technique and future prospects 165
E. K. Abdalla, M. E. Hicks and J. N. Vauthey

Positron emission tomography and colorectal cancer 176
T. H. A. Arulampalam, D. C. Costa, M. Loizidou, D. Visvikis, P. J. Ell and I. Taylor

Systematic review

Somatostatin and octreotide in the prevention of postoperative pancreatic complications and the treatment of enterocutaneous pancreatic fistulas: a systematic review of randomized controlled trials 190
J. Li-Ling and M. Irving

Randomized clinical trials

Randomized clinical trial of laparoscopic *versus* open appendicectomy 200
A. G. Pedersen, O. B. Petersen, P. Wara, H. Rønning, N. Qvist and S. Laurberg

Randomized clinical trial of *Helicobacter pylori* from dental plaque (short note) 206
A. K. Butt, A. A. Khan, B. A. Suleman and R. Bedi

Original articles

Treatment of ruptured hepatocellular adenoma 207
T. Terkivatan, J. H. W. de Wilt, R. A. de Man, R. R. van Rijn, H. W. Tilanus and J. N. M. IJzermans

Improving operative safety for cirrhotic liver resection 210
C.-C. Wu, D.-C. Yeh, M.-C. Lin, T.-J. Liu and F.-K. P'eng

Activation peptide of carboxypeptidase B and anionic trypsinogen as early predictors of the severity of acute pancreatitis 216
S. Appelros, U. Petersson, S. Toh, C. Johnson and A. Borgström

Procalcitonin strip test in the early detection of severe acute pancreatitis 222
M.-L. Kylänpää-Bäck, A. Takala, E. Kemppainen, P. Puolakkainen, R. Haapiainen and H. Repo

Inhibition of matrix metalloproteinases enhances breaking strength of colonic anastomoses in an experimental model 228
I. Syk, M. S. Ågren, D. Adawi and B. Jeppsson

Tumour necrosis factor inhibitors reduce the acute-phase response in hapten-induced colitis 235
A. M. Armstrong, R. Foulkes, G. Jennings, C. Gannon, S. J. Kirk and K. R. Gardiner

Transvaginal repair of pouch-vaginal fistula 241
D. Burke, C. J. H. M. van Laarhoven, F. Herbst and R. J. Nicholls

Sodium hyaluronate enhances colorectal tumour cell metastatic potential *in vitro* and *in vivo* 246
B. Tan, J. H. Wang, Q. D. Wu, W. O. Kirwan and H. P. Redmond

A normal appendix found during diagnostic laparoscopy should not be removed 251
W. T. van den Broek, A. B. Bijnen, P. de Ruiter and D. J. Gouma

Acute-phase protein response, survival and tumour recurrence in patients with colorectal cancer 255
S. J. Wigmore, A. J. McMahon, C. M. Sturgeon and K. C. H. Fearon

Influence of aspirin on early allograft thrombosis and chronic allograft nephropathy following renal transplantation 261
G. J. Murphy, R. Taha, D. C. Windmill, M. Metcalfe and M. L. Nicholson

Perioperative blood transfusions, with or without allogeneic leucocytes, relate to survival, not to cancer recurrence 267
L. M. G. van de Watering, A. Brand, J. G. A. Houbiers, W. M. Klein Kranenbarg, J. Hermans, C. J. H. van de Velde for the Cancer Recurrence and Blood transfusion (CRAB) study group

Reduction of postoperative morbidity and mortality in patients with rectal cancer following the introduction of a colorectal unit 273
K. Smedh, L. Olsson, H. Johansson, C. Åberg and M. Andersson

One-year survey of carcinoma of the oesophagus and stomach in Wales 278
J. K. Pye, M. K. H. Crumplin, J. Charles, R. Kerwat, M. E. Foster and A. Biffin on behalf of hospital clinicians in Wales

Reduction of experimental adhesion formation by inhibition of plasminogen activator inhibitor type 1 286
K. Falk, P. Bjorquist, M. Stromqvist and L. Holmdahl

Review of current practice to establish success after vasectomy 290
H. D. Bradshaw, D. J. Rosario, M. J. James and N. R. Boucher

Incidence of acquired immune deficiency syndrome (AIDS)-related disorders at laparotomy in patients with AIDS 294
A. J. Chambers and R. S. A. Lord

Effect of CD4$^+$ and CD8$^+$ cell depletion on wound healing 298
P. A. Davis, D. J. Corless, R. Aspinall and C. Wastell

Sentinel nodes outside lymph node basins in patients with melanoma 305
G. K. Roozendaal, J. D. H. de Vries, D. van Poll, L. Jansen, H. Schraffordt Koops, O. E. Nieweg and B. B. R. Kroon

Standards of documentation of the surgeon-patient consultation in current surgical practice 309
K. J. Fernando and A. K. Siriwardena

Correspondence 313

Book reviews 316

Scientific surgery 318

Instructions to authors 319

Number 3

Leading article

Sentinel lymph node biopsy in the management of thyroid disease 321
J. L. Pasieka

Clinical dilemma

Varicose veins and pregnancy 323
L. de Cossart

Reviews

Laparoscopy in the staging of pancreatic cancer 325
P. W. T. Pisters, J. E. Lee, J. N. Vauthey, C. Charnsangavej and D. B. Evans

Preoperative (neoadjuvant) chemoradiotherapy in oesophageal cancer 338
J. I. Geh, A. M. Crellin and R. Glynne-Jones

Randomized clinical trials

Randomized clinical trial of local bupivacaine perfusion *versus* parenteral morphine infusion for pain relief after laparotomy 357
W. K. Cheong, F. Seow-Choen, K. W. Eu, C. L. Tang and S. M. Heah

Stoma-related complications are more frequent after transverse colostomy than loop ileostomy: a prospective randomized clinical trial 360
D. P. Edwards, A. Leppington-Clarke, R. Sexton, R. J. Heald and B. J. Moran

Original articles

Treatment strategy for patients with middle and lower third bile duct cancer 364
T. Todoroki, T. Kawamoto, N. Koike, K. Fukao, J. Shoda and H. Takahashi

Impact of laparoscopic surgery on experimental hepatic metastases 371
C. N. Gutt, V. Riemer, Z. G. Kim, J. Erceg and M. Lorenz

Clinicopathological features and treatment of intraductal papillary mucinous tumour of the pancreas 376
M. Falconi, R. Salvia, C. Bassi, G. Zamboni, G. Talamini and P. Pederzoli

Epidemiology of abdominal aortic aneurysms in the Asian community 382
J. I. Spark, J. L. Baker, P. Vowden and D. Wilkinson

Preliminary study of D-dimer as a possible marker of acute bowel ischaemia 385
S. Acosta, T. K. Nilsson and M. Björck

Value of intraoperative duplex imaging during supervised carotid endarterectomy 389
T. S. Padayachee, M. D. Brooks, C. L. McGuinness, K. B. Modaresi, J. A. C. Arnold and P. R. Taylor

Nitric oxide prevents intestinal mitochondrial dysfunction induced by surgical stress 393
S. Thomas, R. Anup, P. Susama and K. A. Balasubramanian

Outcome and late functional results after anastomotic leakage following mesorectal excision for rectal cancer 400
A. Nesbakken, K. Nygaard and O. C. Lunde

Scintigraphic assessment of colonic transit in women with slow-transit constipation arising *de novo* and following pelvic surgery or childbirth 405
S. M. Scott, C. H. Knowles, M. Newell, N. Garvie, N. S. Williams and P. J. Lunniss

Blockade of growth factor receptors in ductal carcinoma *in situ* inhibits epithelial proliferation 412
K. C. Chan, W. F. Knox, A. Gandhi, D. J. Slamon, C. S. Potten and N. J. Bundred

Clinical significance of mutator phenotype and chromosome 17p and 18q allelic loss in gastric cancer 419
G. de Manzoni, A. Tomezzoli, A. Di Leo, P. S. Moore, G. Talamini and A. Scarpa

Lymph node micrometastasis and prognosis in patients with oesophageal squamous cell carcinoma 426
F. Sato, Y. Shimada, Z. Li, G. Watanabe, M. Maeda and M. Imamura

Gastrointestinal complications in lung transplant survivors that require surgical intervention 433
H. J. Hoekstra, K. Hawkins, W. J. de Boer, K. Rottier and W. van der Bij

Other primary cancers occurring after treatment of superficial oesophageal cancer 439
A. Kokawa, H. Yamaguchi, Y. Tachimori, H. Kato, H. Watanabe and Y. Nakanishi

Evaluation of the necessity for gastrectomy with lymph node dissection for patients with submucosal invasive gastric cancer 444
T. Gotoda, M. Sasako, H. Ono, H. Katai, T. Sano and T. Shimoda

Local heat-shock priming-induced improvement in microvascular perfusion in osteomyocutaneous flaps is mediated by heat-shock protein 32 450
M. Rücker, T. Schäfer, F. Roesken, W. J. Spitzer, M. Bauer and M. D. Menger

Extensive surgical cytoreduction and intraoperative hyperthermic intraperitoneal chemotherapy in patients with pseudomyxoma peritonei 458
A. J. Witkamp, E. de Bree, M. M. Kaag, G. W. van Slooten, F. van Coevorden and F. A. N. Zoetmulder

Role of tumour necrosis factor in lung injury caused by intestinal ischaemia–reperfusion 464
C. Köksoy, M. A. Kuzu, I. Kuzu, H. Ergün and I. Gürhan

Correspondence 469

Erratum 472

Book reviews 473

Scientific surgery 474

Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland abstracts 475

Instructions to authors 479

Number 4

Leading article

Phaeochromocytoma in pregnancy 481
L. M. Brunt

Clinical dilemma

Provision of long-term vascular access for haemodialysis in a patient with exhausted superficial arm veins 484
M. L. Nicholson

Reviews

Dysphagia after antireflux surgery 486
V. L. Wills and D. R. Hunt

Management of aortic aneurysm in the presence of a horseshoe kidney 500
O. B. Stroosma, G. Kootstra and G. W. H. Schurink

Randomized clinical trial

Single-blind randomized clinical trial of laparoscopic *versus* open appendicectomy in children 510
H. Lintula, H. Kokki and K. Vanamo

Original articles

Prognostic factors and survival after hepatic resection for hepatocellular carcinoma without cirrhosis 515
N. Nagasue, T. Ono, A. Yamanoi, H. Kohno, O. N. El-Assal, H. Tamura and M. Uchida

Sympathetic autoregulation in peripheral vascular disease 523
K. T. Delis, A. F. Lennox, A. N. Nicolaides and J. H. Wolfe

Variation in clinical decision making is a partial explanation for geographical variation in lower extremity amputation rates 529
J. Connelly, M. Airey and S. Chell

Fate of hypertension after repair of coarctation of the aorta in adults 536
M. A. Bhat, K. S. Neelakandhan, M. Unnikrishnan, R. S. Rathore, M. P. Mohan Singh and G. N. Lone

Immune-stimulating effects of low-dose perioperative recombinant granulocyte–macrophage colony-stimulating factor in patients operated on for primary colorectal carcinoma 539
A. K. Mels, M. G. Statius Muller, P. A. M. van Leeuwen, B. M. E. von Blomberg, R. J. Scheper, M. A. Cuesta, R. H. J. Beelen and S. Meijer

Decreased tyrosine kinase C expression may reflect developmental abnormalities in Hirschsprung's disease and idiopathic slow-transit constipation 545
P. Facer, C. H. Knowles, P. K. Thomas, P. K. H. Tam, N. S. Williams and P. Anand

Topical diltiazem ointment in the treatment of chronic anal fissure 553
J. S. Knight, M. Birks and R. Farouk

Expression of the *RET* proto-oncogene in papillary thyroid carcinoma and its correlation with clinical outcome 557
P. Kjellman, D. L. Learoyd, M. Messina, G. Weber, A. Hoog, G. Wallin, C. Larsson, B. G. Robinson and J. Zedenius

Expression of gastrin in developing gastric adenocarcinoma 564
M. Henwood, P. A. Clarke, A. M. Smith and S. A. Watson

Analysis and surgical treatment of persistent dysphagia after Nissen fundoplication 569
J. E. Bais, B. P. L. Wijnhoven, A. A. M. Masclee, A. J. P. M. Smout and H. G. Gooszen

Laparoscopic antireflux surgery in the treatment of the acid-sensitive oesophagus 577
M. I. Booth, J. Stratford, E. Thompson and T. C. B. Dehn

Determinants of death following burn injury 583
M. J. Muller, S. P. Pegg and M. R. Rule

Leptin and its relation to weight loss, *ob* gene expression and the acute-phase response in surgical patients 588
A. G. W. Moses, N. Dowidar, B. Holloway, I. Waddell, K. C. H. Fearon and J. A. Ross

Correspondence 594

Book reviews 596

Scientific surgery 597

Vascular Surgical Society of Great Britain and Ireland abstracts 598

Instructions to authors 623

Number 5

Leading article

Screening for abdominal aortic aneurysm 625
J. S. Lindholt

Clinical dilemma

An unexpected liver secondary 627
P. Balladur and R. Parc

Reviews

Oesophageal diverticula 629
M. L. Thomas, A. A. Anthony, B. G. Fosh, J. G. Finch and G. J. Maddern

Quality of life as an outcome measure in surgical oncology 643
B. S. Langenhoff, P. F. M. Krabbe, T. Wobbes and T. J. M. Ruers

Randomized clinical trials

Cost–utility analysis of open *versus* laparoscopic groin hernia repair: results from a multicentre randomized clinical trial 653
Medical Research Council Laparoscopic Groin Hernia Trial Group

Randomized, dose-finding phase III study of lithium gamolenate in patients with advanced pancreatic adenocarcinoma 662
C. D. Johnson, M. Puntis, N. Davidson, S. Todd and R. Bryce

Prospective randomized multicentre trial comparing stapled with open haemorrhoidectomy 669
E. Ganio, D. F. Altomare, F. Gabrielli, G. Milito and S. Canuti

Original articles

Early gallbladder carcinoma does not warrant radical resection 675
T. Wakai, Y. Shirai, N. Yokoyama, S. Nagakura, H. Watanabe and K. Hatakeyama

Plasma trypsinogen activation peptide in patients with acute pancreatitis (short note) 679
E. Kemppainen, J. Mayer, P. Puolakkainen, M. Raraty, J. Slavin and J. P. Neoptolemos

Clinicopathological study of hepatocellular carcinoma with diaphragmatic involvement (short note) 681
K. F. Leung, A. K. K. Chui, K. L. Leung, P. B. S. Lai, C. T. Liew and W. Y. Lau

Revisiting transtibial amputation with the long posterior flap 683
P. A. Allcock and A. S. Jain

In-hospital mortality from abdominal aortic surgery in Great Britain and Ireland: Vascular Anaesthesia Society audit 687
P. J. M. Bayly, J. N. S. Matthews, P. M. Dobson, M. L. Price and D. G. Thomas

Prospective study of primary anastomosis following sigmoid resection for suspected acute complicated diverticular disease 693
A. W. Gooszen, R. A. E. M. Tollenaar, R. H. Geelkerken, H. J. Smeets, W. A. Bemelman, P. Van Schaardenburgh and H. G. Gooszen

Endoscopic axillary surgery in breast cancer 698
T. Kuehn, C. Santjohanser, D. Grab, W. Klauss, K. Koretz and R. Kreienberg

Sentinel node biopsy with technetium-99m colloidal rhenium sulphide in patients with breast cancer 704
T. Watanabe, I. Kimijima, T. Ohtake, A. Tsuchiya, F. Shishido and S. Takenoshita

Unique clinical characteristics of primary hyperparathyroidism in India 708
S. K. Mishra, G. Agarwal, D. K. Kar, S. K. Gupta, A. Mithal and J. Rastad

Prospective analysis of the diagnostic yield of extended *en bloc* resection for adenocarcinoma of the oesophagus or gastric cardia 715
J. B. F. Hulscher, J. W. Van Sandick, G. J. A. Offerhaus, H. W. Tilanus, H. Obertop and J. J. B. Van Lanschot

Contralateral groin exploration is not justified in infants with a unilateral inguinal hernia 720
A. Ballantyne, G. Jawaheer and F. D. Munro

Percutaneous endoscopic gastrostomy in patients with ventriculoperitoneal shunts 724
A. L. Taylor, T. A. Carroll, J. Jakubowski and G. O'Reilly

Correspondence 728

Book reviews 731

Scientific surgery 732

Surgical Research Society abstracts 733

Instructions to authors 767

Number 6

Leading articles

Ethics in surgical practice 769
J. M. Little

Resection margins in Crohn's disease 771
B. G. Wolff

Review

Haemobilia 773
M. H. A. Green, R. M. Duell, C. D. Johnson and N. V. Jamieson

Systematic review

Systematic review of antiplatelet therapy for the prevention of myocardial infarction, stroke or vascular death in patients with peripheral vascular disease 787
P. Robless, D. P. Mikhailidis and G. Stansby

Randomized clinical trial

Randomized clinical trial of the effect of open *versus* laparoscopically assisted colectomy on systemic immunity in patients with colorectal cancer 801
C.-L. Tang, K.-W. Eu, B.-C. Tai, J. G. S. Soh, D. Machin and F. Seow-Choen

Original articles

Management of 155 patients with benign liver tumours 808
C. K. Charny, W. R. Jarnagin, L. H. Schwartz, H. S. Frommeyer, R. P. DeMatteo, Y. Fong and L. H. Blumgart

Botulinum toxin injection is an effective treatment for axillary hyperhidrosis (short note) 814
P. J. Whatling and J. Collin

Microcirculatory effects of experimental acute limb ischaemia–reperfusion 816
R. Dammers, X. H. T. Wehrens, M. G. A. oude Egbrink, D. W. Slaaf, H. A. J. M. Kurvers and G. Ramsay

Recombinant soluble P-selectin glycoprotein ligand 1 moderates local and remote injuries following experimental lower-torso ischaemia 825
C. Kyriakides, J. Favuzza, Y. Wang, W. G. Austen Jr, F. D. Moore Jr and H. B. Hechtman

Use of a minilaparotomy in the treatment of colonic cancer 831
T. Nakagoe, T. Sawai, T. Tsuji and H. Ayabe

Randomized study to examine the value of on-table inspection of the appendix musosa (short note) 837
A. N. Charlton, N. E. New and G. J. Pettigrew

Tumour location and the effects of preoperative radiotherapy in the treatment of rectal cancer 839
T. Holm, H. Johansson, L. E. Rutqvist and B. Cedermark

Long-term results of treating hepatic colorectal metastases with cryosurgery 844
T. J. M. Ruers, J. Joosten, G. J. Jager and T. Wobbes

Follow-up confirms sustained benefit of circumferential stapled anoplasty in the management of prolapsing haemorrhoids 850
G. C. Beattie and M. A. Loudon

Endocoil magnetic resonance imaging quantification of external anal sphincter atrophy 853
A. B. Williams, C. I. Bartram, D. Modhwadia, T. Nicholls, S. Halligan, M. A. Kamm, R. J. Nicholls and W. A. Kmiot

Probability of axillary node involvement in patients with tubular carcinoma of the breast 860
G. Papadatos, A. M. Rangan, T. Psarianos, O. Ung, R. Taylor and J. Boyages

Prediction of prognosis by echocardiography in patients with midgut carcinoid syndrome 865
G. Westberg, B. Wängberg, H. Ahlman, C. H. Bergh, M. Beckman-Suurküla and K. Caidahl

Risk factors for complications following resection of large gastric cancer 873
K. Yasuda, N. Shiraishi, Y. Adachi, M. Inomata, K. Sato and S. Kitano

Endotoxin, cytokines and lipid peroxides in children with intussusception 878
I. E. Willetts, P. Kite, G. R. Barclay, R. E. Banks, A. Rumley, V. Allgar and M. D. Stringer

Totally extraperitoneal endoscopic repair of recurrent inguinal hernia 884
J. A. van der Hem, J. F. Hamming, J. D. Meeuwis and H. J. M. Oostvogel

Correspondence 887

Book reviews 892

Scientific surgery 894

Instructions to authors 895

Number 7

Leading articles

Ethics of surgical innovation 897
G. Gillett

Medical negligence and the law 899
P. J. Maughan

Systematic review

Systematic review and meta-analysis of emergency ultrasonography for blunt abdominal trauma 901
D. Stengel, K. Bauwens, J. Sehouli, F. Porzsolt, G. Rademacher, S. Mutze and A. Ekkernkamp

Meta-analysis

Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery 913
P. Mismetti, S. Laporte, J.-Y. Darmon, A. Buchmüller and H. Decousus

Randomized clinical trial

Prospective randomized trial of polypropylene mesh compared with nylon darn in inguinal hernia repair 931
A. Koukourou, W. Lyon, J. Rice and D. A. Wattchow

Vascular Surgical Society

Provocation of experimental aortic inflammation and dilatation by inflammatory mediators and *Chlamydia pneumoniae* 935
J. Tambiah, I. J. Franklin, N. Trendell-Smith, D. Peston and J. T. Powell

A single normal ultrasonographic scan at age 65 years rules out significant aneurysm disease for life in men 941
P. Crow, E. Shaw, J. J. Earnshaw, K. R. Poskitt, M. R. Whyman and B. P. Heather

Association between plaque instability, angiogenesis and symptomatic carotid occlusive disease 945
R. Mofidi, T. B. Crotty, P. McCarthy, S. J. Sheehan, D. Mehigan and T. V. Keaveny

Differences in the detection of cyclo-oxygenase 1 and 2 proteins in symptomatic and asymptomatic carotid plaques 951
S. M. Wijeyaratne, C. R. Abbott, S. Homer-Vanniasinkam, A. I. D. Mavor and M. J. Gough

Portsmouth POSSUM models for abdominal aortic aneurysm surgery 958
D. R. Prytherch, G. L. Sutton and J. R. Boyle

Performance indicators from routine hospital data: death following aortic surgery as a potential measure of quality of care 964
K. A. Rigby, S. Palfreyman and J. A. Michaels

Original articles

Clinicopathological factors predicting outcome after resection of mass-forming intrahepatic cholangiocarcinoma 969
T. Uenishi, K. Hirohashi, S. Kubo, T. Yamamoto, O. Yamazaki and H. Kinoshita

Late mortality in patients with severe acute pancreatitis 975
B. Gloor, C. A. Müller, M. Worni, M. E. Martignoni, W. Uhl and M. W. Büchler

Resection rate and effect of postoperative chemotherapy on survival after surgery for colorectal liver metastases 980
J. Figueras, C. Valls, A. Rafecas, J. Fabregat, E. Ramos and E. Jaurrieta

Gamma-glutamyl transpeptidase messenger RNA may serve as a diagnostic aid in hepatocellular carcinoma (short note) 986
K.-S. Jeng, I.-S. Sheen and Y.-C. Tsai

Patterns of pelvic invasion are prognostic in the treatment of locally recurrent rectal cancer 988
K. Yamada, T. Ishizawa, K. Niwa, Y. Chuman, S. Akiba and T. Aikou

Criteria for extramural perineural invasion as a prognostic factor in rectal cancer 994
H. Ueno, K. Hase and H. Mochizuki

Randomized study of coagulation and fibrinolysis during and after gasless and conventional laparoscopic cholecystectomy 1001
J. F. Larsen, P. Ejstrud, F. Svendsen, F. Redke, V. Pedersen and H. B. Rahr

Outcome and resource utilization in gastroenterological surgery 1006
M. Lång, M. Niskanen, P. Miettinen, E. Alhava and J. Takala

Correspondence 1015

Book reviews 1020

Corrigendum 1021

Scientific surgery 1022

Instructions to authors 1023

Number 8

Leading articles

Doctors and the law – a personal view 1025
J. N. Johnson

Risk management 1027
A. E. Young

Reviews

Clinical and economic evaluation of surgical treatments for faecal incontinence 1029
A. J. Malouf, M. G. Chambers and M. A. Kamm

Anorectal injury following pelvic radiotherapy 1037
D. Hayne, C. J. Vaizey and P. B. Boulos

Randomized clinical trials

Randomized clinical trial of stapled *versus* Milligan–Morgan haemorroidectomy 1049
R. Shalaby and A. Desoky

Effect of *Helicobacter pylori* eradication on the ulcer recurrence rate after simple closure of perforated duodenal ulcer: retrospective and prospective randomized controlled studies 1054
V. Kate, N. Ananthakrishnan and S. Badrinath

Randomized study comparing cardiac response in endovascular and open abdominal aortic aneurysm repair 1059
P. W. M. Cuypers, M. Gardien, J. Buth, C. H. Peels, J. A. Charbon and W. C. J. Hop

Randomized double-blind controlled trial of roxithromycin for prevention of abdominal aortic aneurysm expansion 1066
S. Vammen, J. S. Lindholt, L. Østergaard, H. Fasting and E. W. Henneberg

Original articles

Non-operative management of haemobilia 1073
J. Moodley, B. Singh, S. Lalloo, S. Pershad and J. V. Robbs

Experience with laparoscopic ultrasonography for defining tumour resectability in carcinoma of the pancreatic head and periampullary region 1077
A. M. Taylor, S. A. Roberts and J. McK. Manson

Liver regeneration after major hepatectomy for biliary cancer 1084
M. Nagino, M. Ando, J. Kamiya, K. Uesaka, T. Sano and Y. Nimura

Gender differences in long-term survival of patients with colorectal cancer 1092
M. W. Wichmann, C. Muller, H. M. Hornung, U. Lau-Werner, F. W. Schildberg and the Colorectal Cancer Study Group

Road traffic fatalities in Victoria, Australia and changes to the trauma care system 1099
F. T. McDermott, S. M. Cordner, A. B. Tremayne and the Consultative Committee on Road Traffic Fatalities

Effect of multimodality therapy on circulating vascular endothelial growth factor levels in patients with oesophageal cancer 1105
C. O. McDonnell, J. H. Harmey, D. J. Bouchier-Hayes and T. N. Walsh

Effect of oesophagectomy on monocyte-induced apoptosis of peripheral blood T lymphocytes 1110
K. Kono, A. Takahashi, H. Iizuka, H. Fujii, T. Sekikawa and Y. Matsumoto

Role of fundoplication in patient symptomatology after laparoscopic antireflux surgery 1117
A. C. de Beaux, D. I. Watson, C. O'Boyle and G. G. Jamieson

Chronic pain and quality of life following open inguinal hernia repair 1122
A. S. Poobalan, J. Bruce, P. M. King, W. A. Chambers, Z. H. Krukowski and W. C. S. Smith

Correspondence 1127

Book reviews 1135

Scientific surgery 1137

Surgical Infection Society of Europe abstracts 1138

Instructions to authors 1151

Number 9

Leading articles

Postoperative futility: a clinical algorithm for setting limits 1153
L. B. McCullough and J. W. Jones

Confidentiality and healthcare 1155
J. McEwen

Systematic review

Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery 1157
J. Bruce, Z. H. Krukowski, G. Al-Khairy, E. M. Russell and K. G. M. Park

Review

Penetrating atherosclerotic ulcers of the aorta 1169
M. Troxler, A. I. D. Mavor and S. Homer-Vanniasinkam

Randomized clinical trials

Prospective randomized double-blind placebo-controlled trial of glyceryl trinitrate in endoscopic retrograde cholangiopancreatography-induced pancreatitis 1178
S. Sudhindran, E. Bromwich and P. R. Edwards

Randomized clinical trial comparing totally extraperitoneal inguinal hernia repair with the Shouldice technique 1183
W. R. Fleming, T. B. Elliott, R. McL. Jones and K. J. Hardy

Original articles

Expression of inducible nitric oxide synthase contributes to the development of pancreatitis following pancreatic ischaemia and reperfusion 1189
K. Ayub, F. Serracino-Inglott, R. C. N. Williamson and R. T. Mathie

Liver transplantation for early-detected, multifocal hepatocellular carcinoma (short note) 1194
M. Salizzoni, F. Zamboni, F. Lupo, A. Franchello, E. David and M. Rizzetto

Comparison of cardiac troponin I and creatine kinase ratios in the detection of myocardial injury after aortic surgery 1196
P. C. Haggart, D. J. Adam, P. F. Ludman and A. W. Bradbury

Preservation of endothelial integrity and function in experimental vascular anastomosis with non-penetrating clips 1201
C. Zeebregts, J. van den Dungen, H. Buikema, A. Tiebosch, J. van der Want and R. van Schilfgaarde

Preserved endothelial integrity and nitric oxide synthase in saphenous vein grafts harvested by a 'no-touch' technique 1209
J. C. S. Tsui, D. S. R. Souza, D. Filbey, V. Bomfim and M. R. Dashwood

Quality of life after low anterior resection with total mesorectal excision and temporary loop ileostomy for rectal carcinoma 1216
D. P. O'Leary, C. J. Fide, C. Foy and M. E. Lucarotti

Population-based study of factors influencing occurrence and prognosis of local recurrence after surgery for rectal cancer 1221
S. Manfredi, A. M. Benhamiche, B. Meny, N. Cheynel, P. Rat and J. Faivre

Patient accuracy of reporting on hereditary non-polyposis colorectal cancer-related malignancy in family members 1228
N. Katballe, S. Juul, M. Christensen, T. F. Ørntoft, F. P. Wikman and S. Laurberg

Diagnosis and prognosis of breast cancer by magnetic resonance spectroscopy of fine-needle aspirates analysed using a statistical classification strategy 1234
C. E. Mountford, R. L. Somorjai, P. Malycha, L. Gluch, C. Lean, P. Russell, B. Barraclough, D. Gillett, U. Himmelreich, B. Dolenko, A. E. Nikulin and I. C. P. Smith

Pattern of cervical lymph node metastases from papillary carcinoma of the thyroid 1241
R. Sivanandan and K. C. Soo

Intragastric balloon in the treatment of patients with morbid obesity 1245
J. D. Evans and M. H. Scott

Epidemiological study of oesophageal and gastric cancer in south-east England 1249
H. M. Kocher, K. Linklater, S. Patel and J. P. M. Ellul

Glove powder promotes adhesion formation and facilitates tumour cell adhesion and growth 1258
M. P. van den Tol, R. Haverlag, M. E. E. van Rossen, F. Bonthuis, R. L. Marquet and J. Jeekel

Correspondence 1264

Book reviews 1269

Scientific surgery 1271

British Association of Endocrine Surgeons abstracts 1272

Instructions to authors 1279

Number 10

Leading articles

Endovascular treatment of abdominal aortic aneurysm: a failed experiment 1281
J. Collin and J. A. Murie

Ethics of consent to surgical treatment 1283
T. Bates

Systematic review

Systematic review of randomized clinical trials of surgical treatment for carpal tunnel syndrome 1285
A. A. M. Gerritsen, B. M. J. Uitdehaag, D. van Geldere, R. J. P. M. Scholten, H. C. W. de Vet and L. M. Bouter

Reviews

Effect of laparoscopy on immune function 1296
A. Gupta and D. I. Watson

Detection and clinical significance of occult tumour cells in colorectal cancer 1307
G. Tsavellas, H. Patel and T. G. Allen-Mersh

Randomized trial

Randomized clinical trial comparing suture and mesh repair of umbilical hernia in adults 1321
A. Arroyo, P. García, F. Pérez, J. Andreu, F. Candela and R. Calpena

Association of Surgeons

Extent of ductal carcinoma *in situ* within and surrounding invasive primary breast carcinoma 1324
N. Crombie, R. S. Rampaul, S. E. Pinder, C. W. Elston, J. F. R. Robertson and I. O. Ellis

Rising incidence of post-transplant lymphoproliferative disease in kidney transplant recipients 1330
G. Libertiny, C. J. E. Watson, D. W. R. Gray, K. I. Welsh and P. J. Morris

Pro- and anti-inflammatory cytokine release in open *versus* endovascular repair of abdominal aortic aneurysm 1335
T. E. Rowlands and S. Homer-Vanniasinkam

Community mortality after ruptured abdominal aortic aneurysm is unrelated to the distance from the surgical centre 1341
K. Cassar, D. J. Godden and J. L. Duncan

Value of POSSUM physiology scoring to assess outcome after intra-arterial thrombolysis for acute leg ischaemia (short note) 1344
B. Neary, B. Whitman, C. Foy, B. P. Heather and J. J. Earnshaw

Diagnosis and management of a mediastinal leak following radical oesophagectomy 1346
S. M. Griffin, P. J. Lamb, S. M. Dresner, D. L. Richardson and N. Hayes

Non-operative management of the primary tumour in patients with incurable stage IV colorectal cancer 1352
A. I. Sarela, J. A. Guthrie, M. T. Seymour, E. Ride, P. J. Guillou and D. S. O'Riordain

Prevention of the neoplastic progression of Barrett's oesophagus by endoscopic argon beam plasma ablation 1357
C. D. Morris, J. P. Byrne, G. R. A. Armstrong and S. E. A. Attwood

Randomized clinical trial of intravenous fluid replacement during bowel preparation for surgery 1363
G. Sanders, S. J. Mercer, K. Saeb-Parsey, M. A. Akhavani, K. B. Hosie and A. W. Lambert

Original articles

Effects of adenosine on ischaemia–reperfusion injury associated with rat pancreas transplantation 1366
F. Pi, F. Badosa, A. Sola, J. Roselló Catafau, C. Xaus, N. Prats, E. Gelpí and G. Hotter

Reintervention as a clinical trial endpoint after peripheral arterial bypass surgery 1376
H. R. Watson, G. Belcher and M. Horrocks

Outcome of surgical treatment for carotid body paraganglioma 1382
J. T. M. Plukker, E. P. Brongers, A. Vermey, A. Krikke and J. J. A. M. van den Dungen

Small bowel obstruction after appendicectomy 1387
R. E. B. Andersson

Strategy for the surgical management of patients with idiopathic megarectum and megacolon 1392
C. B. Ó Súilleabháin, J. H. Anderson, R. F. McKee and I. G. Finlay

Hospital caseload and the results achieved in patients with rectal cancer 1397
F. Marusch, A. Koch, U. Schmidt, M. Pross, I. Gastinger and H. Lippert

Prospective controlled trial of a standardized meal stimulation test in the detection of pancreaticoduodenal endocrine tumours in patients with multiple endocrine neoplasia type 1 1403
P. Langer, A. Wild, I. Celik, I. Kopp, A. Bergenfelz and D. K. Bartsch

Influence of the number of lymph nodes examined on staging of gastric cancer 1408
H. K. Lee, H.-K. Yang, W. H. Kim, K. U. Lee, K. J. Choe and J.-P. Kim

Survey of the use of thromboprophylaxis in laparoscopic surgery in Denmark 1413
T. Filtenborg Tvedskov, M. S. Rasmussen and P. Wille-Jørgensen

Correspondence 1417

Book reviews 1420

Scientific surgery 1422

Instructions to authors 1423

Number 11

Leading articles

Irritable bowel syndrome: new horizons in pathophysiology and treatment 1425
M. Bose and M. J. G. Farthing

Present and future management of deep vein thrombosis 1427
B. D. Braithwaite

Reviews

Molecular mechanisms of renal allograft fibrosis 1429
J. R. Waller and M. L. Nicholson

Management of thoracic duct injuries after oesophagectomy 1442
S. A. Wemyss-Holden, B. Launois and G. J. Maddern

Randomized trials

Randomized trial assessing anal sphincter injuries after stapled haemorrhoidectomy 1449
Y.-H. Ho, F. Seow-Choen, C. Tsang and K.-W. Eu

Randomized controlled multicentre trial of somatostatin infusion after pancreaticoduodenectomy 1456
C. Gouillat, J. Chipponi, J. Baulieux, C. Partensky, J. Saric and B. Gayat

Original articles

Value of lymph node dissection during resection of intrahepatic cholangiocarcinoma 1463
M. Shimada, Y. Yamashita, S. Aishima, K. Shirabe, K. Takenaka and K. Sugimachi

Readmissions after pancreatoduodenectomy 1467
R. C. I. van Geenen, T. M. van Gulik, O. R. C. Busch, L. T. de Wit, H. Obertop and D. J. Gouma

Cystatin C deficiency is associated with the progression of small abdominal aortic aneurysms 1472
J. S. Lindholt, E. J. Erlandsen and E. W. Henneberg

Methodology and reporting in studies of local recurrence after curative excision of the rectum for cancer 1476
O. F. Dent, P. H. Chapuis, E. L. Bokey and R. C. Newland

Multicentre retrospective analysis of the outcome of artificial anal sphincter implantation for severe faecal incontinence 1481
D. F. Altomare, G. Dodi, F. La Torre, G. Romano, E. Melega and M. Rinaldi

Long-term effects of stapled haemorrhoidectomy on internal anal function and sensitivity 1487
D. F. Altomare, M. Rinaldi, P. L. Sallustio, P. Martino, M. De Fazio and V. Memeo

Ileoanal pouch function is related to postprandial pouch tone 1492
J. Steens, W. A. Bemelman, W. J. H. J. Meijerink, G. Griffioen, R. A. van Hogezand and A. A. M. Masclee

Normal gastrointestinal transit after colonic resection using epidural analgesia, enforced oral nutrition and laxative 1498
L. Basse, J. L. Madsen and H. Kehlet

Total mesorectal excision preserves male genital function compared with conventional rectal cancer surgery 1501
C. A. Maurer, K. Z'graggen, P. Renzulli, M. K. Schilling, P. Netzer and M. W. Büchler

Anatomy of the anal canal and perianal structures as defined by phased-array magnetic resonance imaging 1506
G. L. Morren, R. G. H. Beets-Tan and J. M. A. van Engelshoven

Estimating the benefits of adjuvant systemic therapy for women with early breast cancer 1513
M. Grogan, L. Tabar, B. Chua, H.-H. Chen and J. Boyages

Prospective study of the effect of laparoscopic Nissen fundoplication on reflux mechanisms 1519
J. W. A. Straathof, J. Ringers and A. A. M. Masclee

Validity of surgical simulation for the assessment of operative skill 1525
A. M. Paisley, the late P. J. Baldwin and S. Paterson-Brown

'Fast track' postoperative management protocol for patients with high co-morbidity undergoing complex abdominal and pelvic colorectal surgery 1533
C. P. Delaney, V. W. Fazio, A. J. Senagore, B. Robinson, A. L. Halverson and F. H. Remzi

Conservative management of appendix mass in children 1539
J. Gillick, M. Velayudham and P. Puri

Correspondence 1543

Book reviews 1549

Scientific surgery 1550

Instructions to authors 1551

Number 12

Leading articles

Haemoglobin solutions in surgery 1553
G. J. Vlahakes

Preoperative radiotherapy for rectal cancer 1556
C. A. M. Marijnen and C. J. H. van de Velde

Reviews

Immune therapy in inflammatory bowel disease and models of colitis 1558
B. Singh, F. Powrie and N. J. McC. Mortensen

Suspected acute appendicitis: trends in management over 30 years 1570
P. F. Jones

Randomized trial

Randomized clinical trial of patient-controlled *versus* fixed regimen feeding after elective abdominal surgery 1578
I. J. M. Han-Geurts, J. Jeekel, H. W. Tilanus and K. J. Brouwer

Original articles

Role of the neutrophil in the development of systemic inflammatory response syndrome and sepsis following abdominal aortic surgery 1583
J. I. Spark and D. J. A. Scott

Risk modelling study for carotid endarterectomy 1590
G. Kuhan, E. D. Gardiner, A. F. Abidia, I. C. Chetter, P. M. Renwick, B. F. Johnson, A. R. Wilkinson and P. T. McCollum

Diverticular disease of the colon in Accra, Ghana (short note) 1595
B. N. Baako

Plasma concentration of tissue inhibitor of matrix metalloproteinase 1 in patients with colorectal carcinoma 1596
N. Yukawa, T. Yoshikawa, M. Akaike, Y. Sugimasa, S. Takemiya, S. Yanoma, Y. Noguchi and Y. Takanashi

Salvage abdominal surgery in patients with a retained rectal stump after restorative proctocolectomy and stapled anastomosis 1602
H. Tulchinsky, J. S. McCourtney, K. V. Subba Rao, W. Chambers, J. Williams, K. H. Wilkinson and R. J. Nicholls

Impact of total mesorectal excision on the results of surgery of distal rectal cancer 1607
W. L. Law and K. W. Chu

Systemic levels of glyceryl trinitrate following topical application to the anoderm do not correlate with the measured reduction in anal pressure 1613
M. Jonas, D. A. Barrett, P. N. Shaw and J. H. Scholefield

Prospective analysis of quality of life and survival following mesorectal excision for rectal cancer 1617
J. Camilleri-Brennan and R. J. C. Steele

Function of a colonic J pouch continues to improve with time 1623
G. J. C. Harris, I. C. Lavery and V. W. Fazio

Non-invasive methods of assessing angiogenesis and their value in predicting response to treatment in colorectal cancer 1628
M. L. George, A. S. K. Dzik-Jurasz, A. R. Padhani, G. Brown, D. M. Tait, S. A. Eccles and R. I. Swift

Ileal neoappendicostomy for antegrade colonic irrigation (short note) 1637
P. Christensen, S. Buntzen, K. Krogh and S. Laurberg

Treatment of 100 patients with sentinel node-negative breast cancer without further axillary dissection 1639
R. M. H. Roumen, G. P. Kuijt, I. H. Liem and M. W. P. M. van Beek

Multicentre study of detection and false-negative rates in sentinel node biopsy for breast cancer 1644
L. Bergkvist, J. Frisell, G. Liljegren, F. Celebioglu, S. Damm and M. Thorn

Response of atypical symptoms of gastro-oesophageal reflux to antireflux surgery 1649
T. M. Farrell, W. S. Richardson, T. L. Trus, C. D. Smith and J. G. Hunter

Correspondence 1653

Book reviews 1656

Scientific surgery 1658

Instructions to authors 1659

Author index 1661

Subject index 1666

Referee index 1677

British Journal of Surgery

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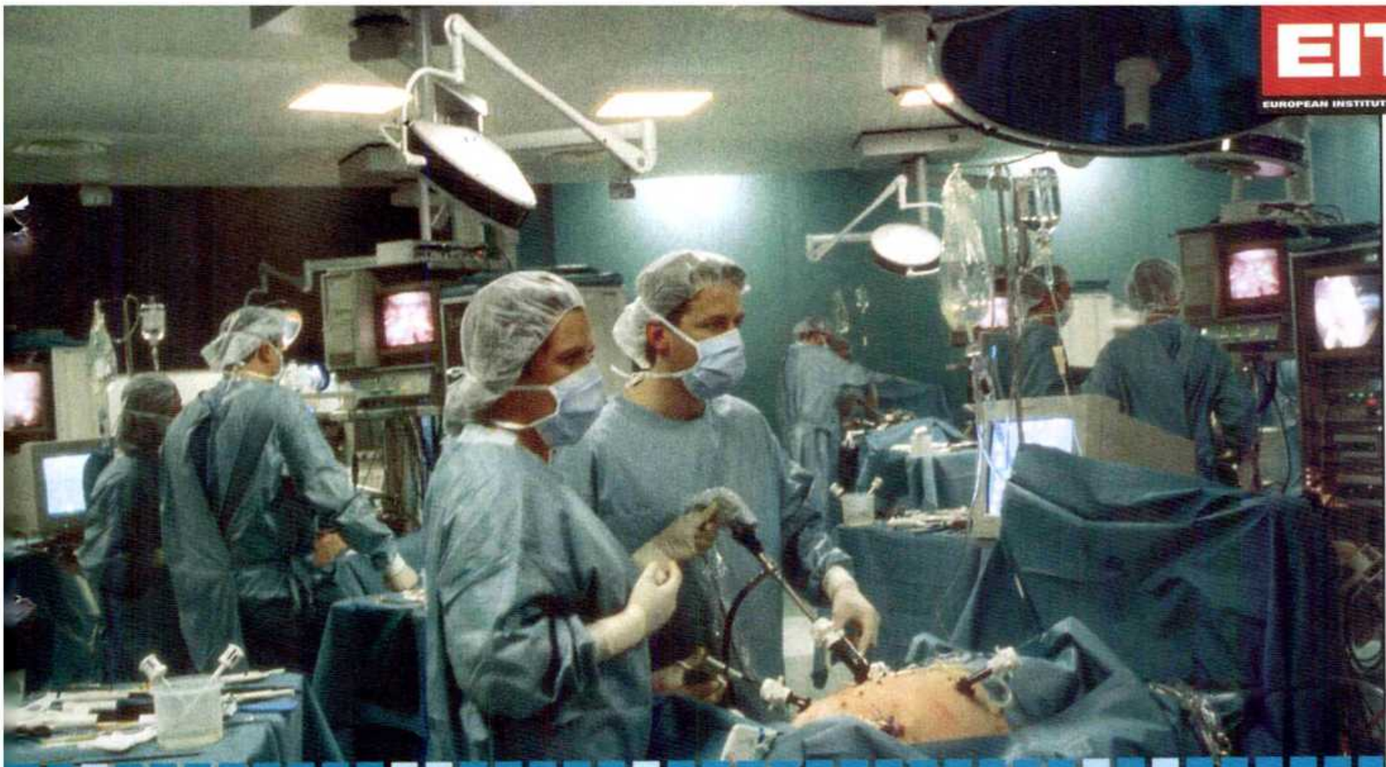

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Contents

British Journal of Surgery

Volume 89, Issue 2, February 2002

Leading articles

129 **Underpowered studies**
R. Lilford and A. J. Stevens
The case is made for the publication of small unbiased studies

132 **General surgery training crisis in America**
H. Sanfey
The world of surgery has changed

Review

134 **Litigation for pneumothorax as a complication of fine-needle aspiration of the breast**
T. Bates, T. Davidson and R. E. Mansel
Not usually negligent

Systematic review

138 **Systematic review of dynamic graciloplasty in the treatment of faecal incontinence**
A. E. Chapman, B. Geerdes, P. Hewett, J. Young, T. Eyers, G. Kiroff and G. J. Maddern
Complications are the cost of continence

Randomized trial

154 **Randomized clinical trial of Ligasure™ *versus* open haemorrhoidectomy**
F. F. Palazzo, D. L. Francis and M. A. Clifton
Bloodless haemorrhoidectomy may be better

Original articles

158 **Long-term results of bilateral thoracoscopic splanchnicectomy in patients with chronic pancreatitis**
H. C. J. L. Buscher, J. B. M. J. Jansen, R. van Dongen, R. P. Bleichrodt and H. van Goor
Half the patients develop recurrent pain

163 **Serum amyloid A is a better early predictor of severity than C-reactive protein in acute pancreatitis**
J. M. Mayer, M. Raraty, J. Slavin, E. Kemppainen, J. Fitzpatrick, A. Hietaranta, P. Puolakkainen, H. G Beger and J. P. Neoptolemos
Serum amyloid A is a better early predictor of severity

172 **Role of mast cells in the development of pancreatitis-induced multiple organ dysfunction**
M. Dib, X. Zhao, X. D. Wang and R. Andersson
Mast cell activation is involved in endothelial dysfunction in experimental acute pancreatitis

179 **Extensive surgery for carcinoma of the gallbladder**
S. Kondo, Y. Nimura, N. Hayakawa, J. Kamiya, M Nagino and K. Uesaka
Radical resection of stage III and IV disease is required to ensure complete tumour excision

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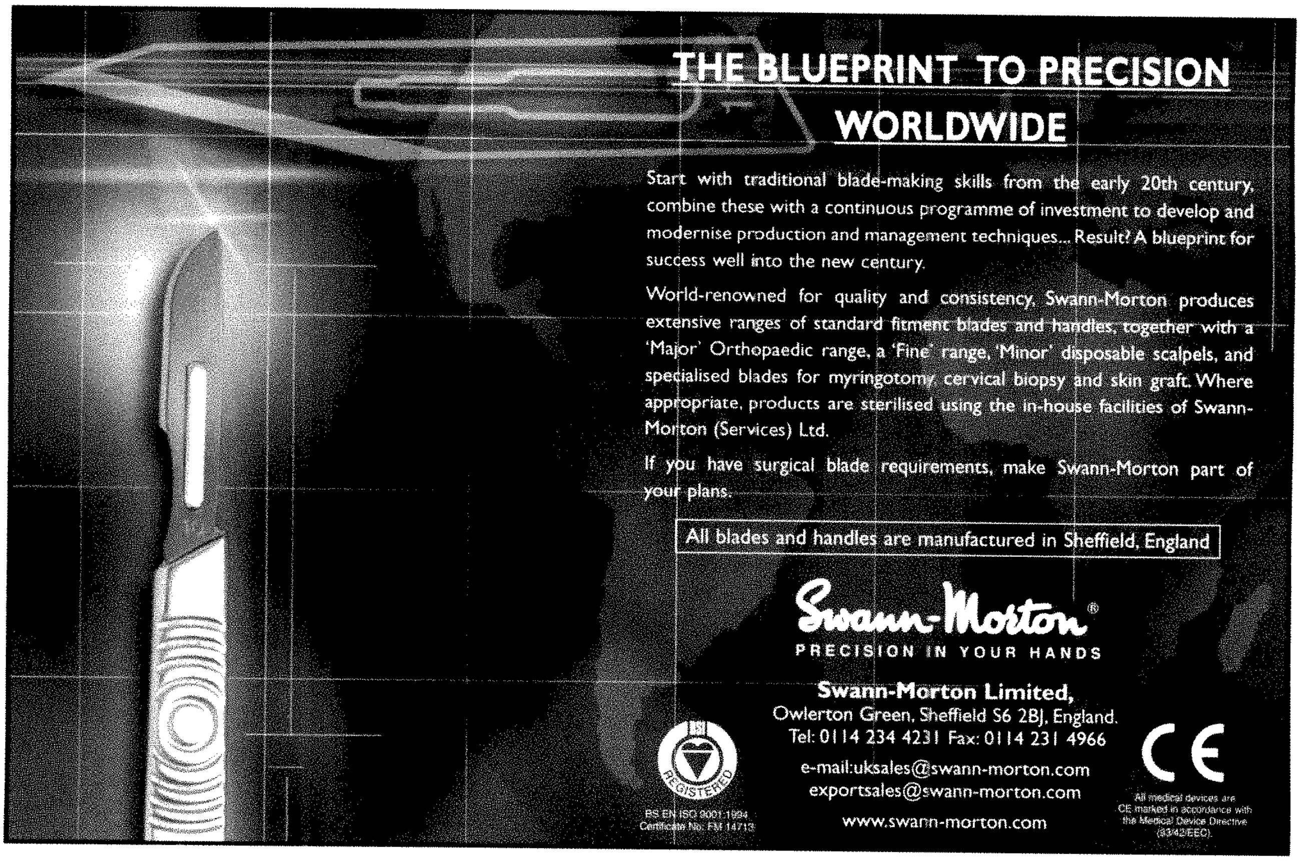

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185 **Effects of experimental lower-limb ischaemia–reperfusion injury on the mesenteric microcirculation**
X. H. T. Wehrens, E. V. Rouwet, M. G. A. oude Egbrink, D. W. Slaaf and G. Ramsay
Reperfusion significantly reduced splanchnic blood flow

192 **Comparison of colour Doppler ultrasonography, ascending phlebography and clinical examination in the diagnosis of incompetent calf perforating veins (short note)**
G. Antoch, S. Pourhassan, O. Hansen and W. Stock
Clinical examination with duplex imaging was optimal

194 **Outcome after septic complications in J pouch procedures**
U. A. Heuschen, E. H. Allemeyer, U. Hinz, M. Lucas, C. Herfarth and G. Heuschen
Repeated salvage attempts are worthwhile

201 **Evidence for separate disease phenotypes in intestinal Crohn's disease**
N. R. Borley, N. J. McC. Mortensen, M. A. Chaudry, S. Mohammed, T. Clarke and D. P. Jewell
Disease phenotyping is not valuable

206 **Cancer recurrence along the pouch longitudinal suture line after colonic J pouch–anal anastomosis (short note)**
N. Dehni, S. Caplin, P. Frileux, R. Sarkis and R. Parc
Local recurrence can occur in the pouch

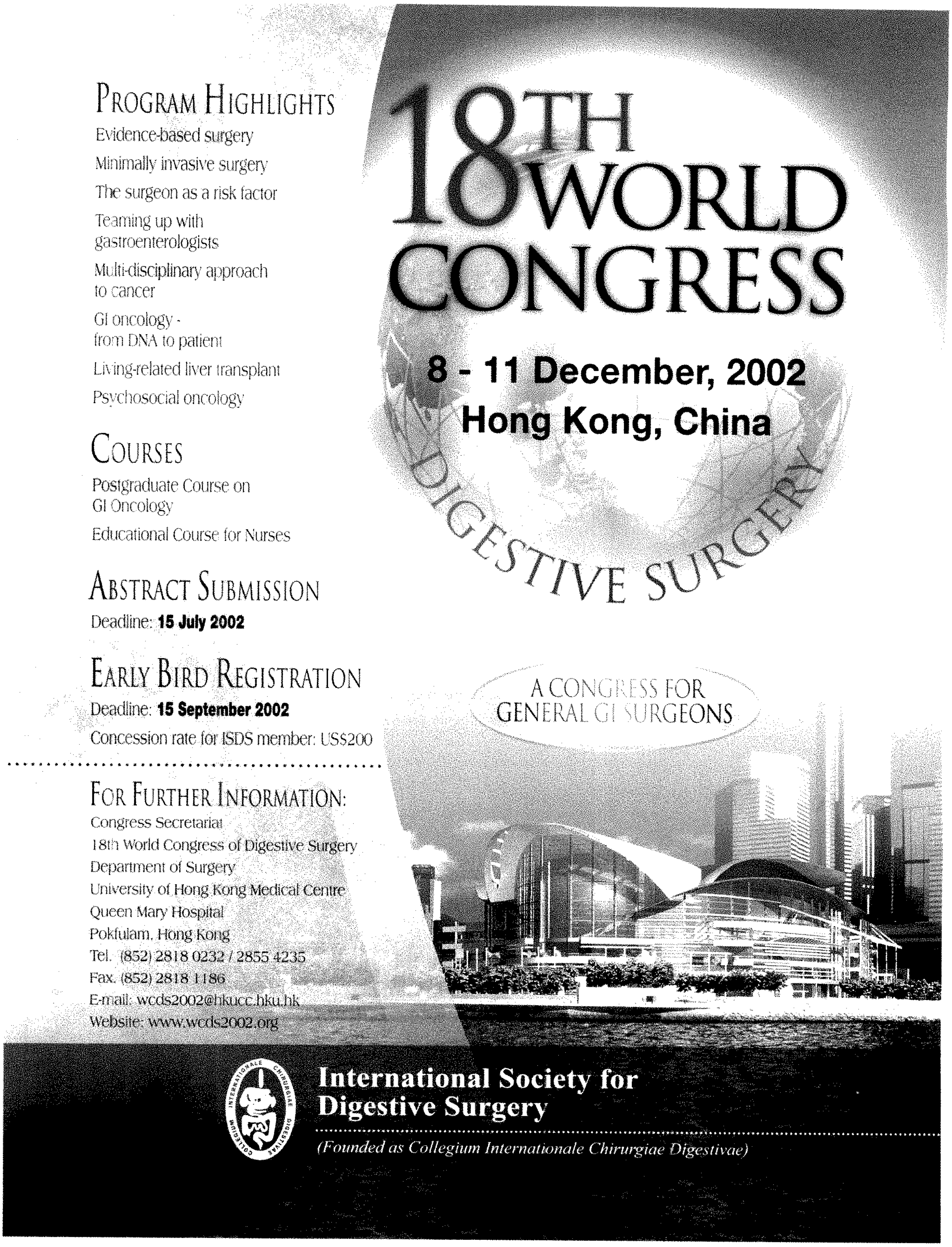
208 **Cytoreduction including total gastrectomy for pseudomyxoma peritonei**
P. H. Sugarbaker
Extensive surgery for a rare disease

213 **Significance of immunohistochemical nodal micrometastasis as a prognostic indicator in potentially curable oesophageal carcinoma**
S. Komukai, T. Nishimaki, T. Suzuki, T. Kanda, S. Kuwabara and K. Hatakeyama
Immunohistochemistry may modify staging of lymph nodes

220 **Length of the antral segment in pylorus-preserving gastrectomy**
Y. Nakane, T. Michiura, K. Inoue, M. Sato, K. Nakai and K. Yamamichi
Increasing the length of antrum retained may improve pyloric function

225 **Long-term results of antireflux surgery indicate the need for a randomized clinical trial**
R. Sandbu, H. Khamis, S. Gustavsson and U. Haglund
Treatment failures twice as common with the laparoscopic approach

231 **Endoscopic ultrasonography in the diagnosis and management of suspected upper gastrointestinal submucosal tumours**
E. F. Shen, I. D. R. Arnott, J. Plevris and I. D. Penman
Endoscopic ultrasonography may reveal unsuspected findings



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236 **Abnomal expression of E-cadherin and β-catenin may be a molecular marker of submucosal invasion and lymph node metastasis in early gastric cancer**
M. Tanaka, Y. Kitajima, G. Edakuni, S. Sato and K. Miyazaki
Potentially clinically useful marker

245 **Correspondence**

249 **Book reviews**

254 **Scientific surgery**

255 **Instructions to authors**

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Candidates for these scholarships should apply to the Honorary Secretary of the AESGBI (Mr David Hay) at The Royal College Surgeons of England, 35-43 Lincoln's Inn Fields, London WC2A 3PE. Candidates wishing to be considered for both types of scholarship must make separate applications for each one. The deadline for receipt of applications is 1st March 2002. The names of successful applicants will be announced at the Association of Surgeons meeting in May 2002 in Dublin.

Leading article

Underpowered studies

R. Lilford and A. J. Stevens

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It is frequently argued that underpowered trials are unethical, that they are poor science and unreliable, and that journal editors should not publish them[1]. How has the negativity towards small trials arisen?

Clinical research over the past half century, and in particular since Cochrane's persuasive report, has been transformed by the rise of the clinical (randomized controlled) trial[2]. From a small handful of such trials completed by 1950, there are now in excess of 30 000 on the Cochrane Controlled Trials register, many of them in surgery[3]. This growth has had a number of consequences. One is the pressure on journal space. A second is the preponderance of topics for which any clinical difference found between compared treatments is unlikely to be large. A third is the development of a basket of tools and criteria with which to judge the design, conduct and reporting of trials[4].

One of the key criteria by which trials have been judged is sample size. In the absence of a striking difference between treatments (or between treatment and placebo) small trials are likely to be underpowered. Small trials are also, sometimes, poor trials. So what is the point of publishing a trial which is 'too small'? At best, it could be argued that this is a waste of space and, at worst, something that might mislead. They might be wrong (if they are poor) or encourage one to confuse 'evidence of no effect' with 'no evidence of effect' (if they are just underpowered). Indeed, the argument could be extended along the lines that publication of such 'inadequately' powered studies would act as an incentive to researchers and sponsors to conduct or fund such inconclusive studies; refusal to publish would encourage better behaviour. However, there are many problems with the arguments that support the out of hand rejection of trial reports based on small studies.

Two crucial distinctions will set the scene. The first is between those factors that affect the reliability of clinical studies and contribute to the criteria for assessment: accuracy and precision. An inaccurate study is one which is subject to bias such that the association between the putative explanatory variable (type of treatment) and the outcome is distorted. Lack of blinding, poor randomization, and excluding people from one arm of a study but not another can all bias results. Biased results are a serious threat to scientific integrity that typically lead to substantial overestimates of treatment effects[5]. The authors lend no support to their publication. However, lack of precision is a different matter altogether. Here, the effect is measured within wide confidence limits. This only means that, even if there is a real effect, it is likely to be missed using conventional statistical testing. Note that power is really a function of the number of events that occur in a study. By a small trial, what is really meant is a trial that is small in relation to the frequency of occurrence of the outcome of interest.

The second distinction is between small trials and poor trials. It is possible that the circumstances which lead to trials being small, such as short-term research funding or non-cooperation of recruitment staff, might also lead to trials being poorly designed, and there is some evidence that small trials tend to be of lower quality than large. However, the argument that this should preclude their publication is specious. The other criteria – essentially, whether the treatments were truly randomly allocated, whether all the patients were accounted for, and whether the outcomes were assessed blind (even in surgical trials) – all deal with this problem. Therefore, the fact that small trials are of lower quality ***on average*** does not justify a refusal to publish a ***particular*** small trial that has cleared the usual quality threshold. In any case, the quality of small trials is likely to improve as their protocols come under prospective external scrutiny and as a result of initiatives in the governance of research. But, should authors publish small trials of high quality? The main argument against is that they may be misinterpreted, so that a null result is confused with evidence of no effect. This argument must be offset against others that suggest that failure to publish small trials would do more harm than good.

Single trials seldom make the case for a change in policy, even when large. It would be pretentious of authors or editors to regard all but the most exceptional articles as the final word on a topic. The development of meta-analytic techniques to synthesize multiple trial results means that reports on single trials can more safely be regarded as contributions to the world literature and do not make a case in isolation. Publication, even of large trials, can be most realistically viewed as a contribution to a topic.

In some cases it may be unnecessary or even damaging to wait for large trials. The historical cumulative meta-analysis of trials on treatments for myocardial infarction showed that the first ten trials of thrombolysis had yielded conclusive proof by 1972 of the role of streptokinase, yet it would take another 16 years for the Second International Study of Infarct Survival to put the matter to rest in a single study[6]. In other cases small trials may be critical for informing practice, because even many highly cited multicentre trials are of insufficient size to demonstrate clinical effects that would be sufficient to change practice. For example, consider the trials on the effect of aspirin for the prevention of pre-eclampsia and perinatal loss. Even the large Collaborative Low-dose Aspirin Study in Pregnancy (CLASP) trial of 8000 women at moderate risk was inadequate to show an (important) 20 per cent reduction in perinatal mortality rate because of the relative rarity of the outcomes of interest[7]. Only by combining many such studies has it been possible to measure effects with an appropriate precision[8]. Thus, although the improvement shown in the CLASP study was 'not statistically significant', by combining this and multiple other studies a clinically important effect has been confirmed within conventional limits of statistical precision. In the case of rare diseases, the only way that *any* unbiased measurements of effectiveness can be made is by trials of limited statistical power. It has been argued that such studies are best analysed by Bayesian methods[9].

Furthermore, there is no obvious definition of an 'underpowered' study. An appropriately powered study is one that can detect the clinically important effect[10]. However, since different patients and different doctors wish to make different trade-offs, the minimal important clinical effect will vary from person to person. It follows that a study which is sufficiently powerful for one person (i.e. which would exclude the clinically important effect for that person) might be inadequately powered for another.

A serious corollary of failure to publish articles on the grounds that they are 'underpowered' is 'publication bias' – the tendency for negative results to elude publication or, if they are published, to be published after long delays and in journals with low citation rates[11]. If editors choose to reject small studies for publication, there must be an onus on them to make sure that rejection on size grounds applies whether the results are positive and exciting or negative and dull. It is doubtful that such consistency is achieved. Indeed the funnel plot technique of detecting publication bias is based on the knowledge that editors do not behave in such an even-handed way.

Finally, the argument that the publication of small trials would be too expensive can be overcome by electronic publication of full articles, with short summaries in paper form (as practised by some journals). Alternatively, papers could be accepted by purely on-line journals, or authors could simply make their results and methodology available to investigators carrying out systematic reviews, such as those in the Cochrane collaboration. Indeed, knowledge of the existence of small trials will soon be enhanced through the Cochrane international registry of clinical trials[3]; it is a tenet of good research governance that all research findings should be made publicly available. It is certainly not a tenet that this should only happen if the studies are of a certain size.

In conclusion, the argument that small trials are bad science and so should not be published is unhelpful. At the limit almost all individual trials are too small, and yet progress has been made in medicine by looking for confirmation and by narrowing overall confidence limits through quantitative meta-analysis. Failure to accept smaller articles for publication must leave the world with a less precise overall estimate than would otherwise have been available, the very problem that rejection of small trials is supposed to avoid. Patients who are invited to participate in small trials are therefore being asked to contribute to the pool of world knowledge. In the case of treatments for serious diseases, they should only enter such studies when, having been informed as fully as possible about current evidence, they have no preference between treatments, that is, when they are in equipoise. In other words, patients with serious diseases should not lose out in prospect by taking part in trials[12]. Provided this requirement is followed and patients realize that other trials may be needed to answer a question to everyone's satisfaction, there is no moral argument against offering people entry into these studies[13]. Seen in this light, publication of small unbiased studies is not only permissible, but an obligation that editors should follow scrupulously.

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General surgery training crisis in America

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The results of the 2001 general surgery national residency match revealed a totally unprecedented 68 (7 per cent) unfilled first-year general surgery training positions in the USA. This confirmed a trend noted in recent years towards a decreased interest in surgical careers among graduating medical students, with a corresponding increase in the number of students selecting specialties with controllable lifestyles[1]. In addition, there is currently a 20 per cent attrition rate in general surgery compared with 12 per cent in 1993[2]; residents often leave after 1 or 2 years to pursue less intense surgical subspecialties[3]. This suggests failure in the selection process or in fulfilment of the career expectations of the residents, and is an important commentary on the career counselling that takes place in medical schools. Although general surgery is now one of the least competitive surgical specialties, programme directors have not noted any objective change in the quality of applicants[4]; non-US graduates currently comprise 15–17 per cent of general surgery training slots[5].

The reasons behind this trend, which sparked considerable debate in the surgical literature and was the main topic of conversation at the 2001 American College of Surgeons meeting, are multifactorial. They include institutional promotion of primary care disciplines, decreasing reimbursement, a 30 per cent or more reduction in time spent by medical students on surgical rotations, and unfavourable perceptions of the surgical lifestyle. While some of the issues pertaining to job satisfaction are unique to the American system, others represent global change in how care is delivered in the new millennium. They may reflect a change in the public's respect for the medical profession in general and the greater emphasis on litigation and medical errors. The result is an increasing challenge to surgical educators to attract medical school graduates to a career in surgery. In the USA it is tempting to attribute this decline to an increased emphasis on primary care. In 1999, for the fourth year in a row, more than 50 per cent of medical students entered primary care training. Today, in several states financial incentives are provided to individual trainees and/or medical schools for personal and institutional commitments to primary care[6]. Furthermore, the 1997 Budget Reconciliation Agreement shifted funding from inpatient (and specialty driven) services to training in non-hospital settings. In the USA medical students often graduate with tuition debts totalling $80 000–100 000, and incentives to enter primary care that include loan repayment have enticed graduates away from surgery.

With increasing emphasis on clinical income and medical centre revenue owing to decreasing Medicare reimbursement, surgeons today have less time for resident and medical student education. Efficiency in the operating room is often achieved at the expense of time spent teaching[5]. A decade ago trainees had the opportunity to see patients in clinic, perform their operations and follow their hospital course to discharge. With a shift towards day-case surgery and resident cross-cover, this continuity of care has been lost, along with much of the job satisfaction. The educational time that surgical trainees need today to spend in training to achieve the goals outlined by the American Board of Surgery is greater than ever. Strict enforcement of working hours and days off leads to a conflict in providing sufficient clinical experience without lengthening surgical training programmes. While other countries have been prepared to decrease the surgical trainee's working week to more acceptable levels, in the USA only programmes mandated by rigid state laws (such as in New York) have agreed that a less than 80-h week is acceptable for training in general surgery[3]. Today's trainees have different values and demand a more balanced lifestyle than those who believed the only thing wrong with every other night-call was that you missed half the good cases[7]. Furthermore, women currently constitute at least half of the graduating medical students but represent only 10 per cent of general surgeons in the USA[8] and only 5 per cent of consultant surgeons in the UK[9]. It is not surprising to see a decrease in the number of students pursuing careers in surgery when our specialty is perceived as unattractive by at least 50 per cent of the workforce. While there is much to favour the structured American residency programme with its defined goals, curriculum and time frame, there is a lack of flexibility compared with the systems in the UK and Ireland. Whereas, in the UK, flexible training is an option for women, this is not so in the USA.

Medical students now spend up to 30 per cent less time in surgical rotations, this time having been allotted to additional ambulatory and primary care experience[6]. With less exposure to working surgeons, students lose the ability to identify with a surgeon mentor. The lifestyle identification that medical students have with careers in surgery is that of the sleep-deprived surgical trainee. Although many of us feel that life during training is more civilized than it once was, it is still intense and demanding. The failure of educational leaders in medical schools to ensure that students appreciate the ultimate satisfaction of the practising surgeon is close to the heart of our failure to continue to attract the best students. The efforts to redress what has become an unbalanced medical student curriculum will require increased effort on the part of surgeons to devote time, preparation and attention to students at an early stage in their training[10].

The world of surgery has changed and we need to consider how this change has altered our ability to teach both medical students and young surgeons. We must re-evaluate the current educational process, including student selection, surgical clerkship experience and surgical training programmes[11], and pay more attention to our responsibilities as career counsellors and teachers. Trainees' educational experience should take priority over service commitment; it is hoped that the current crisis will encourage programme directors to identify ways of reducing working hours without compromising training.

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Litigation for pneumothorax as a complication of fine-needle aspiration of the breast

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Background: Pneumothorax is a rare but recognized complication of diagnostic needle aspiration of the breast. Two recent court cases alleging negligence have reached opposing opinions on very similar findings.

Methods: A Medline literature search was carried out.

Results: The reported incidence of pneumothorax after diagnostic aspiration of the breast in seven series varied between three in 100 and one in 10 000, but the weight of evidence tended towards the latter rate. Two studies reported that the complication is more common in the hands of trainees. It is not always possible to maintain the aspirating needle parallel or tangential to the chest wall. Pleural puncture may be more common than is apparent, and is most common in the tail of the breast in a thin woman.

Conclusion: It is important that breast clinicians are aware of the risk of pneumothorax but, provided proper care has been taken, this complication is not the result of a negligent act.

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Introduction

Pneumothorax occurring as a complication of fine-needle aspiration of breast tissue has been reported regularly in the medical literature over the past 20 years. Orr and Margarey[1] first described three cases in 1978 and, although the site in the breast was not stated, the mechanism of injury in each case was thought to be the aspiration of a thick-walled cyst that initially resisted the passage of a needle. They were of the opinion that 'prevention is simple since the direction of the needle should not be towards the chest wall but tangential to it, entering the lump from the side so that if there is a sudden forward movement of the needle (due to loss of resistance) damage to the pleura and underlying lung will not occur'. Most subsequent authors reporting this complication have repeated this advice[2–6]. It is not a simple matter, however, to maintain the needle parallel or tangential to the chest wall when multiple passes through a solid lesion deep in the breast[7] are taken at different angles. It is important to ensure that a representative sample has been taken from a possible carcinoma in order to avoid a false-negative result[8].

Frequency of the problem

Earlier reports of pneumothorax have probably overestimated the rate of this complication; in 1991 Croce and Montanari[9] reported that 'there are very few complications to fine needle aspiration cytology, and none are severe, with the exception of pneumothorax, which, however, has a frequency of under 3%'. In recent years, with the recognition of pneumothorax as a rare, but recurring, complication of fine-needle aspiration of the breast, a number of breast units have reviewed large series in an attempt to assess the incidence. An Italian series of 74 000 fine-needle aspiration procedures reported pneumothorax as occurring in one in 5700 procedures[2], but a greater frequency has been estimated by Kaufman *et al.*[5] (one in 417) and Gateley *et al.*[4] (one in 1000).

The Edinburgh Breast Unit in its reported series recognized the complication of pneumothorax on three occasions over an 8-year interval during which approximately 8000 aspirations were performed[10]. The Cardiff Breast Unit reported seven cases from the breast clinics of three teaching hospitals over 3 years and concluded that pneumothorax is an accepted but rare complication of fine-needle aspiration of lumps in the breast[4]. The largest report of pneumothorax in an updated Italian review included more than 200 000 fine-needle aspiration procedures, and estimated the rate at 0·01 per cent, or one in 10 000, although the authors conceded that this might be an underestimate because of asymptomatic (or unrecognized) pneumothoraces[11]. Christie and Bates[6] estimated the same order of frequency, although the sample was much smaller.

Importance of technique

To obtain a representative cytological sample from a breast lump, the needle must be passed several times and at varying angles through the lesion. Intuitively, the closer the angle of needle approach is to being parallel with the chest wall, the less likely it is that an overshoot of the needle tip (by a matter of millimetres only with a deep-seated breast lesion) might pierce the intercostal muscles and pleura to cause a pneumothorax. Pulling a mobile lump away from the chest wall should reduce this risk, but is not possible in all deep breast lesions. A show of hands at a recent meeting of breast surgeons indicated that many had accidentally struck a rib in carrying out aspiration of a breast lump. Indeed, some authorities recommend steadying a breast lump against an underlying rib to prevent pleural penetration[10] – not an instruction with which experienced clinicians would feel comfortable. The ribs form a much larger area of the chest wall surface area than the intercostal spaces and it must be partly for this reason that pneumothorax is a relatively rare injury. Furthermore, experience with lung biopsy indicates that pneumothorax is a relatively infrequent complication of pleural puncture; even when it does occur, pleural drainage is not always required[12].

Difficulty may arise with deep central breast lesions where the shortness of the needle (a 21-G or green needle is 3·7 cm in length) precludes reaching and traversing the lesion while maintaining an angle of approach that is close to parallel with the chest wall[13]. Awareness of the potential for injury is possibly the most important safety factor in minimizing the risk of pneumothorax after aspiration cytology; trainees in breast surgery should be made aware of the risk.

Most reported cases of pneumothorax have resulted from aspiration of lumps in the upper outer quadrant or axillary tail of the breast[4,6], although the injury has also been reported in central breast lesions[5,14] and in the upper inner quadrant of thin women with small breasts[2]. Where the breast is separated from the chest wall by the pectoralis major muscle, a deep breast lesion may still be 1 cm or more from the pleura. In a thin woman with a breast lump arising high in the axillary tail, the corresponding distance may be only a few millimetres. Unexpected movement of the patient during the procedure (due to anxiety or lack of prior explanation), or hyperventilation, may increase the risk of inadvertent pneumothorax.

The questions of medical negligence and informed consent may arise because pneumothorax is sufficiently rare that there is a good case for not warning each patient of this complication[6]. Yet when a pneumothorax arises, the patient suffers an immediate, painful and distressing condition that requires emergency admission to hospital and possible further pleural needling. At best this will involve no more than a night or two in hospital and two or three chest radiographs, but at worst it may involve weeks of discomfort. Since a patient has not been forewarned of this rare complication, it is understandable that thoughts of medical negligence arise. Clinicians all have a duty of care to the patient but, unless this accident is caused by an untrained or unsupervised trainee, common sense suggests that a rare but recognized complication of a procedure is due to bad luck rather than a breach of duty. Although a sincere apology is important, in the authors' view it should not be a matter for the courts to settle.

The view of the court

As in many medical negligence cases, the outcome for or against a plaintiff (the patient) may depend more on the courtroom skills of the expert witness in convincing the judge of the scientific facts or, more importantly, of the uncertainties involved.

Unfortunately, an expert who works only for plaintiffs may be more effective in this setting than the real expert in the field. The solicitor for the plaintiff (and for that matter the defence) is still free to shop around for a favourable opinion. The concept that experts should report to the court rather than the plaintiff or the defendant does not yet seem to have taken effect.

A recent leading article by Fischer[15] on the effect of litigation on surgical practice in North America is pertinent to the emerging scene in the UK. It is still a matter of surprise to many doctors that the finding of 'fact' by a judge in a civil court depends on the balance of probabilities or, whether it is more likely than not. Sometimes this is a fine line in an uncertain world and is far removed from the level of proof required in a criminal court. In the latter situation the facts must be established beyond all reasonable doubt and the findings of the court equate to the scientific findings of a clinical trial where the minimum requirement for acceptance would be 95 per cent confidence limits. The judge wants to know from an expert witness: 'What is your opinion in the light of your considerable experience?'. If medicine has learnt anything in the past 20 years it is that the phrase 'in my clinical experience' should be appropriately received with frank scepticism rather than respectful silence. It is not, therefore, surprising that Fischer[15] finds that the facts of a case on the American legal scene may vary with the skill of an attorney.

Two recent court cases in the UK of accidental pneumothorax during diagnostic aspiration cytology of a breast lump (confirming on both occasions a benign cytological diagnosis) reached opposite opinions on very similar findings. In the first case, the court preferred the evidence of the expert for the defence that pneumothorax was a rare but recognized complication of this procedure, and would occasionally occur despite the use of all necessary skill on the part of an operator trained in the procedure. In the second case, the court preferred the evidence of the expert for the plaintiff, who maintained that pneumothorax always occurred as a result of poor technique, where the operator failed to keep the needle tangential to the chest wall. Thus there was a breach of duty of care, and a settlement was awarded on the basis that negligence had occurred.

In civil law the principle of precedence does not apply and the outcomes of previous hearings need not influence the court when a new case is heard. There would seem to have been an element of lottery in whether the finding of the court was that the patient suffered an accident, as opposed to a failure of duty of care.

Fischer estimates that the cost of wasteful medicolegal business incurred in North America may amount to $100 billion; in the UK this currently amounts to 13 per cent of the National Health Service budget. That is not to say that patients who have been damaged by a failure of duty of care should not be compensated. The Woolf reforms will, hopefully, speed the process considerably and reduce the cost of small-value claims that far exceed the money received by the patient. On the other hand, when patients pursue a vexatious or weak claim, usually on legal aid, their lawyers may acquiesce with the continuation of the case if an obliging expert can be found to give sufficient support. When the hospital Trust or defence society successfully defends a claim, there is no recompense of their costs. When a case is lost against reasonable expectation there is great reluctance to throw good public money after bad in mounting an appeal on an important point of principle.

Fine-needle aspiration cytology is an invaluable diagnostic procedure in the breast clinic and an integral part of the triple assessment process that has enabled rapid and accurate diagnosis of breast disease. Whilst an awareness of the potential of pneumothorax by all relevant practitioners, and meticulous attention to technique in training breast specialists, may further reduce the incidence of this complication, it is likely to remain a complication, albeit rare, even when all care is taken. Specific guidelines on training in aspiration cytology techniques are not currently defined, but may require future consideration. Both Dixon[10] and Catania *et al.*[2] suggest that the injury is more common in the hands of trainees; if it became apparent that supervision or training were deficient, an action for damages would not be defensible. Nevertheless, it is apparent that a low rate of pneumothorax is inevitable and, provided the technique is performed by a trained, experienced person, the authors do not believe that there is a case for regarding this rare injury as a negligent act.

The authors have given expert opinion in an action for damages in one or more cases of pneumothorax caused by fine-needle aspiration cytology of the breast, but none has been involved in litigation as defendant or was an expert witness at the time of submission of this article for publication.

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Systematic review of dynamic graciloplasty in the treatment of faecal incontinence

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Background: The aim of this systematic review was to compare the safety and efficacy of dynamic graciloplasty with colostomy for the treatment of faecal incontinence.

Methods: Two search strategies were devised to retrieve literature from the Medline, Current Contents, Embase and Cochrane Library databases up until November 1999. Inclusion of papers depended on a predetermined protocol, independent assessments by two reviewers and a final consensus decision. English language papers were selected. Acceptable study designs included randomized controlled trials, controlled clinical trials and case series. Forty papers met the inclusion criteria. They were tabulated and critically appraised in terms of methodology and design, outcomes, and the possible influence of bias, confounding and chance.

Results: No high-level evidence was available and there were no comparative studies. Mortality rates were around 2 per cent for both graciloplasty and colostomy. Morbidity rates reported for graciloplasty appear to be higher than those for colostomy. Dynamic graciloplasty was clearly effective at restoring continence in between 42 and 85 per cent of patients, whereas colostomy is, by its design, incapable of restoring continence. However, dynamic graciloplasty is associated with a significant risk of reoperation.

Conclusion: While dynamic graciloplasty appears to be associated with a higher rate of complications than colostomy, it is clearly a superior intervention for restoring continence in some patients. It is recommended that a comparative, but non-randomized, study be undertaken to evaluate the safety of dynamic graciloplasty in comparison to colostomy, and that the procedure should be performed only in centres where it is carried out routinely.

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Introduction

Faecal incontinence may be defined as involuntary excretion of stools at an inappropriate time or in an inappropriate place, occurring more than twice in a month[1]. It is an unpleasant and debilitating problem that can profoundly affect personal and social life[2]. The prevalence in the British population has been reported as 4·2 per 1000 in men aged 15–64 years, and 10·9 per 1000 in men aged 65 years or over; in women it is 1·7 and 13·3 per 1000 respectively[1]. In a more recent American report[3] the prevalence was 23 per 1000. This difference reflects an uncertainty that is possibly caused by many patients being reluctant to admit that they are incontinent, and doctors being reluctant to embarrass patients by asking about it[4]. However, when asked specifically the reported information on incontinence is reasonably consistent and can provide reliable prevalence estimates[5]. The direct cost of faecal incontinence is based on prevalence rates, number of incontinent episodes, nursing time, incontinence supplies and laundry requirements; it has been calculated to be US $9771 per patient per year[6]. Costs may also be incurred for treatment of diarrhoea, prevention and treatment of breakdown of skin, increased incidence of female genital infection and bacteriuria, stoma care (where a stoma has been created for incontinence) and loss of productive capacity, but an exact

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The Editors have satisfied themselves that all authors have contributed significantly to this publication

calculation is lacking[7]. Elderly patients constitute the majority of those affected[2,8] and incontinence is often a reason for becoming institutionalized.

Good continence depends on several anatomical, physiological and psychological entities: mental function, stool volume and consistency, colonic transit, rectal distensibility, anal sphincter function, pelvic floor function, anorectal sensation and anorectal reflexes[9]. Deficiency of one, and often more than one, of these entities may lead to incontinence. Since continence is a complex multifactorial process, incontinence may present in various degrees and with different pathophysiologies; treatment must be chosen carefully. The causes of long-standing faecal incontinence may be divided into anorectal malformations, perineal trauma, pudendal nerve lesions and low motor neurone lesions.

Treatment options for faecal incontinence

Most patients can be treated well conservatively. A high-fibre diet or bulk-forming agents to improve stool volume and consistency or the use of cleansing enemas are effective. Biofeedback has proven to be successful in increasing the voluntary contraction amplitude of the external anal sphincter and the pelvic floor[10].

In patients with a mechanical defect of the anal sphincter, overlapping sphincteroplasty is the operation of choice[11] and results in restoration of a normal squeeze pressure[12]. In complicated cases, sphincteroplasty can be combined with a levatorplasty[13] or a transposition of one limb of the puborectal muscle around the anal canal[14]. Postanal repair was introduced by Parks in 1959[15] for the treatment of patients with neurogenic faecal incontinence. When an anterior levatorplasty and an internal sphincter plication are added, the total pelvic floor repair results are improved, with complete continence being achieved in two-thirds of patients[16]. When none of the above treatment modalities is successful, a permanent colostomy may be created, the only other possibility being the creation of a new anal sphincter using an artificial device or autologous tissue.

Musculoplasty

The creation of a new anal sphincter with the use of a free smooth muscle collar is an attractive idea. In contrast to skeletal muscle, smooth muscle is able to maintain a continuous state of contraction for long periods of time. About 10 cm of free, denervated and prestretched large bowel may be folded around the colon stump as a cuff. Good results have been reported[17–19], although it is difficult to understand how continence could be completely reliant on internal sphincter function. Owing to deprivation of circulation, this cuff tends to scar[20].

Transposed skeletal muscles are most widely used for the creation of a new anal sphincter. The precondition is that this muscle should not be essential for locomotion and/or posture. Furthermore, site, muscle mass and the position of the neurovascular bundle should allow easy mobilization and transposition in order to preserve a healthy and functional muscle. Muscles suited to sphinteroplasty are sartorius, gluteus maximus and gracilis.

In animal experiments sartorius has shown excellent results when used to create a new sphincter[21]. In humans, owing to its segmental vascularization which restricts the arch of rotation if the muscle is transposed, it seems to do less well[22].

The gluteus maximus is not important for posture or ordinary walking, but running, climbing stairs and rising from a seated position require its activity[23]. Its choice in the creation of an anal sphincter is a logical one because it is powerful and is often used naturally as an accessory muscle to continence. The use of the gluteus muscle was first reported by Chetwood[24] in 1902 and further developed by Schoemaker[25] and Bistrom[26]. After the Second World War this technique sank into oblivion until it was revived in the 1980s[27–29]; it has had several modifications since then[30,31]. Unlike gracilis, gluteus maximus is an important muscle in daily activities and impairment of function may pose problems for the patient.

Gracilis is the most superficial adductor on the medial side of the thigh, but it has no important function in humans. The possibility of using this muscle for sphintero-plasty was first explored in 1952 by Pickrell[32] in the treatment of children with neurogenic faecal incontinence (spina bifida, meningocele)[33,34]. Stimulated by the results of Stone and McLanahan[35,36] and using fascia strips attached to the glutei, he introduced the anal (and later the urinary)[37] graciloplasty. Because of its superficial position and the proximal neurovascular supply, the muscle is easily accessible and can be dissected free distally without damage. This technique has been applied since 1952 on a wide scale, but with mixed results[20,38–45] because gracilis, like all skeletal muscles, has a majority of type II, fast-twitch, non-fatigue-resistant muscle fibres. These fibres are unable to maintain a sustained contraction.

Dynamic graciloplasty

A normal external anal sphincter has a predominance (80 per cent) of type I, fatigue-resistant, muscle fibres[46]. Only 43 per cent of the muscle fibres in gracilis are type I[46] which explains why this muscle cannot perform a sustained contraction. In 1960 it was found, when the nerve of a type I, slow-twitch, fatigue-resistant muscle was connected to a type II, fast-twitch, fatigue-prone muscle, that these muscle fibres would transform in both directions[47]. It is the motor neurone that determines the physiological, histochemical and biochemical characteristics of the innervated fibres. Later, electrical stimulation of the nerve proved to have the same effect on the muscle[48]. Chronic low-frequency stimulation induces a transformation from fast to slow muscle fibres and chronic high-frequency stimulation from slow to fast muscle fibres[49].

Caldwell[50,51] reported in 1965 the electrical stimulation of the external sphincter with an implantable receiver and an external power supply for the treatment of faecal incontinence and rectal prolapse in children and adults. Reasonable to good results were obtained but problems with the equipment resulted in an eventual failure of the technique. The first electrical stimulation of a transposed gracilis muscle with such a receiver was reported by the paediatric surgeons Dickson and Nixon[52] in 1968, and their goal was to achieve a sustained contraction when stool arrived. Unfortunately, only preliminary data were published. A new avenue in the development of the dynamic graciloplasty was the development of the cardiomyoplasty, electrically stimulated muscle for cardiac assistance[53] and its clinical application[54]. In cardiomyoplasty or aortomyoplasty the latissimus dorsi muscle is wrapped around the heart[55], or the ascending[56] or descending[57] aorta, in order to improve the heart pump in patients with endstage cardiomyopathy.

In 1986 Baeten *et al.*[58] implanted the first neurostimulator in a patient with anal atresia who had been treated with a conventional graciloplasty 10 years before. She had a good active contraction of the gracilis muscle but was still incontinent. The idea was to induce a change from fast-twitch, fatiguable (type II) muscle fibres into slow-twitch, fatigue-resistant (type I) muscle fibres. Active contraction was changed into stimulation-induced contraction. The technique was developed independently by Williams *et al.*[21,59]. Both methods depend on stimulation of the obturator nerve but, while Williams fixes the electrode directly on the nerve, Baeten fixes it intramuscularly, close to the nerve branches inside the muscle[60–63]. The advantage of direct nerve stimulation is the total recruitment of all motor units with the lowest possible energy demand, resulting in a maximum contraction and a prolonged battery life. However, it is questionable whether maximum contraction is necessary or desirable for reasons of potential ischaemic injury to the muscle or colon.

Indications for a dynamic graciloplasty are an external anal sphincter that is damaged beyond repair, a sphincter with severe neurogenic damage and congenital disease, such as anal atresia or spina bifida. In general, dynamic graciloplasty is performed in patients for whom all previous treatment to restore sphincter function has failed. Contraindications are inflammatory bowel disease, and poor motivation or physical or mental incapacity. The presence of a cardiac pacemaker is not necessarily a contraindication but, because the gracilis pulse generator can interfere with the sensing functions of the pacemaker (especially with unipolar stimulation), careful evaluation is required[64]. The average patient accepted for dynamic graciloplasty has a grade V incontinence, has been incontinent for many years, and has had maximal conservative treatment, biofeedback training and one or more previous operations for restoration of continence[63].

Method of dynamic graciloplasty

Systemic antibiotics (metronidazole, gentamicin and flucloxacillin) are administered for 24 h. A urinary catheter is introduced in men. The graciloplasty is performed according to Pickrell *et al.*[33] with several slight modifications. Instead of three small incisions, one large incision is made at the upper thigh (*Fig. 1*). Gracilis is identified, the peripheral arteries are ligated and the muscle is mobilized towards its insertion into the medial aspect of the tibia. A small incision is made below the knee and the distal tendon is cut. The muscle is then further mobilized up to its neurovascular bundle. During the perineal part of the operation, two incisions are made lateral to the anus, one on either side. Three tunnels are made, one posteriorly from the anal canal over the rima ani as high as the coccyx, one anteriorly from the anal canal in the retrovaginal wall (female) or behind the

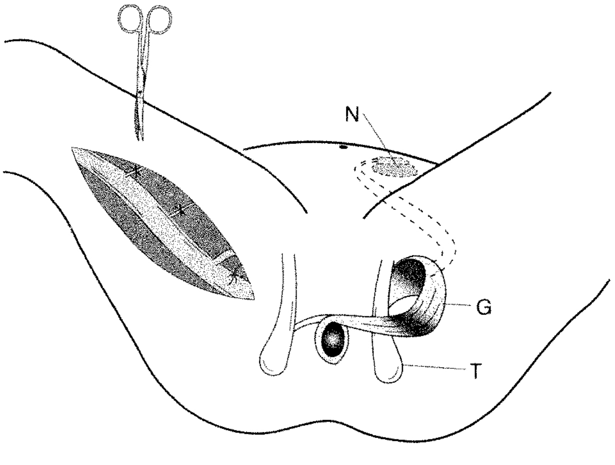

Fig. 1 Mobilization of the right gracilis muscle by ligation of the minor vascular pedicles; proximally the major vascular pedicle and the obturator nerve with its branches are located. On the left side the dynamic graciloplasty configuration is shown after transposition of the muscle and implantation of the stimulation devices. N, neurostimulator; G, gracilis muscle; T, ischial spine

urethra (male) and the third from the perineum to the incision in the leg, passing the strong Scarpa's fascia. This last tunnel should be wide enough easily to accommodate the muscle in order to prevent entrapment, which would endanger muscle blood flow. The muscle is then wrapped around the anal canal, the configuration being determined by the anatomical situation. Most often a gamma loop is used, making the first turn on the frontal side, a second turn on the dorsal side and a third turn on the frontal side again. When there is a large muscle mass or much scar tissue in the rectovaginal septum, the first turn will be on the dorsal side (epsilon loop). When the muscle is not long enough to make one and a half turns the tendon is fixed on the ipsilateral side (alpha loop). The modified alpha or split-sling loop was developed in order to make a perfect circular loop[65]; a hole is made in the mid part of the muscle and the distal part is pulled through. There is some uncertainty as to whether vascularity and/or innervation are endangered by this action. The distal tendon is sutured to the medial side of the ischial spine. Another possibility is fixation to the skin[62]. A protective colostomy is sometimes created. Patients are encouraged to walk the next day and to wear elastic stockings for several weeks.

At first the pacemaker and the leads were implanted 6 weeks after the transposition but implantation now usually occurs at the same time as transposition. All patients have systemic antibiotic prophylaxis for 24 h. At the site of implantation the skin is covered with an iodine-based dressing. An incision is made in the medial aspect of the upper thigh on the site of lowest threshold (located under transcutaneous stimulation before the operation) and an intramuscular flexible coil of platinum iridium wire is introduced as an anode about 4 cm distal to the obturator nerve (towards the anus). With the introduction of a similar electrode, the optimal position for the cathode is determined under electrical stimulation (as close as possible to the intramuscular branches of the nerve). The electrode is then pulled crosswise through the muscle, perpendicular to the muscle fibres, and fixed to the epimysium. The length of the bare surface of the electrode can be adjusted to the diameter of the muscle. Subsequently, the leads are tunnelled subcutaneously to a pocket in the lower abdominal wall and connected to a pulse generator. All implanted devices are soaked in a gentamicin solution and local antibiotics are administered.

Stimulation is typically started 3 days after implantation of the pulse generator, employing a pulse width of 210 μs, a stimulation frequency of 25 pulses per s and a cyclical mode with an 'on' time of 0·1 s and an 'off' time of 1·2 s, yielding a duty cycle of 8 per cent (the time during which the muscle is actually contracting). Subsequently the duty cycle is increased to 14 per cent (0·2 s 'on' and 1·2 s 'off') after 2 weeks, 36 per cent (0·4 s 'on' and 0·7 s 'off') after 4 weeks and 67 per cent (1·0 s 'on' and 0·5 s 'off') after 6 weeks. At 8 weeks continuous stimulation is started. An external magnet is given to all patients to turn the mode of operation of the pulse generator 'off' to permit defaecation and 'on' again after defaecation.

While dynamic graciloplasty offers a good functional result for some patients, it is associated with a high incidence of infection and hardware-related complications. Because of the possibility of high morbidity and uncertain functional effectiveness associated with this complex procedure, Australian Safety and Efficacy Register of New Interventional Procedures-Surgical (ASERNIP-S) undertook a review of its safety and efficacy.

Method

ASERNIP-S review process

Two surgeons familiar with the topic of review (protocol surgeon and invited surgeon) and an ASERNIP-S researcher worked together to draft the protocol for the systematic review and determined the studies to be included. The ASERNIP-S researcher assessed these publications and produced a systematic review, a critique of which was produced by the review group. The review group comprised the advisory (J.Y.) and protocol (P.H.) surgeons, a nominated surgeon (T.E.) from the Colorectal Section of the Royal Australasian College of Surgeons (RACS), a surgeon from another specialty (G.K.), an invited surgeon (B.G.) and an ASERNIP-S researcher (A.E.C.). Once consensus was reached on the recommendations and classifications, they were presented to the ASERNIP-S Management Committee and, subsequently, to the RACS Council for ratification.

Search strategy

Original published studies on dynamic graciloplasty or colostomy for the treatment of faecal incontinence were identified by searching the Medline, Current Contents and Embase databases from 1991 to October 2000. The search terms used were: ((faecal or fecal) and incontin* not (urinary incontin*) and colostomy) or (graciloplast* or (muscle plasty not (cardi* or (gluteal muscle plasty)))), where * is a truncation symbol that retrieves variations of the indicated text, e.g. endoscop* will retrieve the words endoscopy, endoscope, endoscopic, etc. A different, broad strategy was employed for the Cochrane Collection database because the restricted search discovered no references; the simple search term was 'graciloplasty'. Only full peer-reviewed articles were included because abstracts did not provide adequate detail on patient selection, allocation, study design, outcome and measurement methods to allow an accurate, unbiased assessment and comparison of the study results. In addition, the bibliography of each paper included in the review from this initial search was also searched for studies missed in the electronic searches.

Inclusion criteria

Papers were selected for inclusion if they were in English and described randomized controlled trials, controlled clinical trials or case series. Both human and animal studies were included (the former on individuals with faecal incontinence) as long as they related to dynamic graciloplasty and/or to colostomy. All articles were required to provide information on at least one outcome as defined in *Table 1*. Papers dealing with gluteal muscle plasty were excluded, as were those that, in the opinion of the reviewers, represented multiple publications of the same series or were isolated case reports (unless a complication was reported).

Data extraction and analysis

The protocol and invited surgeons and the ASERNIP-S researcher independently assessed articles for suitability using the inclusion criteria, and a consensus was reached about which would be finally included in the study. Unsuitable and duplicate studies were deleted from the literature database. All relevant studies were assessed for level of evidence (*Table 2*), tabulated, and methodologically evaluated for appropriateness of study exclusion criteria, quality of reporting and possible confounding variables. All data and results of statistical tests were extracted from the papers. For particular outcomes, papers were included in the analysis only if they reported specifically on the item of interest; no assumptions were made if data were missing. For example, articles that did not report a complication rate were not assumed to have reported a zero rate; these articles were treated as if the data were missing and so were excluded from all morbidity analyses.

Table 1 Inclusion criteria

Faecal incontinence
Complications
  Systemic infection
  Respiratory complications
  Pulmonary embolism
  Leg pain
  Leg swelling
  Stimulator and lead problems (e.g. breakage or dislocation)
  Wrap complications (tendon displacement, erosion, constipation)
Psychosocial effects
Revision rates (including time to battery replacement)
Mortality rates
Cost-effectiveness
Failure of operation (i.e. stoma for patients with graciloplasty)

Results

The literature search resulted in 37 dynamic graciloplasty and three colostomy studies being retrieved; the latest of the colostomy papers[66] was discovered outside of the search process, but was included because of the paucity of colostomy papers and because of its relevance. All of the papers on graciloplasty were of low-evidence quality. Only one comparative study was found and that compared cost-effectiveness of dynamic graciloplasty with historical colostomy data (level III-3 evidence). The remaining dynamic graciloplasty studies were case series (level IV evidence). Only three colostomy studies were found, of which one reported time-series data, another compared psychosocial outcomes between abdominoperineal resection and anterior resection (level III-2 evidence), and the third was a review of other studies.

There was a large number of studies that might have contributed patient data to more than one paper, although it was generally not possible to determine with certainty where this had occurred. To overcome potential biases that may have resulted from double counting patients, studies were divided into 'primary' and 'secondary' categories (*Table 3*). Data reported in this section all derive from

Table 2 Hierarchy of evidence*

I	Evidence obtained from a systematic review of all relevant randomized controlled trials
II	Evidence obtained from at least one properly designed randomized controlled trial
III-1	Evidence obtained from well designed pseudo-randomized controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomized (cohort studies), case–control studies or interrupted time series with control group
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pretest/post-test

*National Health and Medical Research Council. A designation of levels of evidence. In: 'Guide to the development, implementation and evaluation of clinical practice guidelines'. Commonwealth of Australia. 1999. Appendix B, 52

Table 3 Primary and secondary studies

Primary studies	Secondary studies
Altomare *et al.* (1997)[67]	None
Baeten *et al.* (1995)[63]	Adang *et al.* (1993)[82], Adang *et al.* (1998)[83]*, Baeten *et al.* (1991)[84], Baeten *et al.* (1994)[85], Geerdes *et al.* (1996)[86]*, Konsten *et al.* (1993)[61], Madoff *et al.* (1999)[87]†, Versluis *et al.* (1995)[88]
Baeten *et al.* (2000)[68]	Christiansen *et al.* (1998)[89], Geerdes *et al.* (1996)[86], Madoff *et al.* (1999)[87]†, Mavrantonis *et al.* (1999)[90], Wexner *et al.* (1996)[91]
Cavina *et al.* (1998)[69]	Cavina (1996)[92], Cavina *et al.* (1998)[93]‡, Seccia *et al.* (1994)[62]‡
Geerdes *et al.* (1997)[70]	Geerdes *et al.* (1995)[94], Rongen *et al.* (1999)[95]§
Grumann *et al.* (2001)[66]	None
Hill (1999)[71]	None
Londono-Schimmer *et al.* (1994)[72]	None
Mander *et al.* (1996)[73]	Williams *et al.* (1991)[81]¶
Mander *et al.* (1999)[74]	Kennedy *et al.* (1996)[96], Korsgen and Keighley (1995)[97], Marano *et al.* (1996)[98], Mavrantonis *et al.* (1999)[90], Sielezneff *et al.* (1999)[99], Wexner *et al.* (1996)[91]
Mercati *et al.* (1991)[75]‡	None
Rosen *et al.* (1998)[76]**	Rosen *et al.* (1994)[65], Madoff *et al.* (1999)[87]
Rouanet *et al.* (1999)[77]**	Madoff *et al.* (1999)[87]
Rullier *et al.* (2000)[78]	None
Sprangers *et al.* (1995)[79]	None
Violi *et al.* (1999)[80]	Violi *et al.* (1996)[100]
Williams *et al.* (1991)[81]¶	Mander *et al.* (1996)[73]

*Although this study is more recent than Baeten *et al.* (1995), it shares some of the same patients as Baeten *et al.* (2000), hence Baeten *et al.* (1995) takes precedence. †This study spans both Baeten *et al.* (1995) and Baeten *et al.* (2000), but contributes fewer patients than those two studies together. ‡Many of the patients in this study did not undergo dynamic graciloplasty with an implanted stimulator. §Appears to be a subset of the patients in Geerdes *et al.* (1997). ¶Patients with cancer covered by Mander *et al.* (1996), but data separable for patients without cancer. **Since Madoff *et al.* (1999) was rejected as a primary study because of its overlap with Baeten *et al.* (1995 and 2000), this study (which does not overlap Baeten *et al.*)

'primary' studies, except where clearly unique results are presented in 'secondary' papers. A study was allocated to 'primary' status if it met the following criteria: (1) provided a higher level of evidence according to the National Health and Medical Research Council criteria; (2) maximized the overall sample size; (3) was newer than any potential 'double-counting' study; and (4) did not present a restricted subset of patients reported elsewhere.

Safety

Mortality rates for dynamic graciloplasty ranged from 0 to 31 per cent (*Table 4*). However, some studies included patients suffering from rectal cancer, treated with either abdominoperineal resection or dynamic graciloplasty, in which some deaths were attributable to cancer rather than the dynamic graciloplasty operation. If cancer deaths are excluded from the analysis, mortality rates ranged from 0 to 13 per cent, or an overall rate of 1 (95 per cent confidence interval (c.i.) 1 to 3) per cent). Deaths were due to pulmonary embolism at 8 months (one)[78], cachexia at 3 months (one)[78], myocardial infarction during training (one)[73] and at 2 months (one)[80], and from unspecified causes (two)[68,81]. For colostomy, only one early postoperative mortality rate was available from a single study[72]. The reported rate was 2 (95 per cent c.i. 1 to 4) per cent, or five deaths in a patient pool of 289.

Morbidity events for dynamic graciloplasty ranged from 0·14 to 2·08 per patient, with an overall rate across all primary studies of 1·12 per patient (*Table 5*). This indicates either that most patients suffer some morbidity associated with the procedure or that a few suffer multiple morbidities. In comparison, the equivalent morbidity data in the single colostomy study were initially 0·51 per patient, rising to a cumulative rate of 0·58 per patient at 13 years.

Particular complications are shown in *Table 6*. The commonest for dynamic graciloplasty were infections (28 per cent), problems related to stimulator and lead faults (15 per cent), and leg pain (13 per cent). Battery exhaustion, constipation, anal and body pain, and injury to either or both the gracilis muscle and the colon stump were also reported in over 5 per cent of cases. The calculation of leg and anal pain rates was based on the inclusion of data from Hill[71], and includes all patients who reported any pain, even if not severe. The other rates were calculated without reference to this study[71], which measured only pain. The

Table 4 Mortality rates

Reference	Year	*n*	Deaths	Mortality rate	
				Overall	Excluding cancer
Dynamic graciloplasty					
Altomare *et al.*[67]	1997	9	0	0	
Baeten *et al.*[63]	1995	52	0	0	
Baeten *et al.*[68]	2000	123	1	0·01	
Cavina *et al.*[69]	1998	31	3*	0·10	0·00
Geerdes *et al.*[70]	1997	20	1*	0·05	0·00
Hill[71]	1999	45	n.c.	n.c.	
Mander *et al.*[73]	1996	12	1	0·08	
Mander *et al.*[74]	1999	64	0	0	
Mercati *et al.*[75]	1991	7	0	0	
Rosen *et al.*[76]	1998	28	0	0	
Rouanet *et al.*[77]	1999	9	2*	0·22	0·00
Rullier *et al.*[78]	2000	15	2	0·13	
Violi *et al.*[80]	1999	13	4†	0·31	0·08
Williams *et al.*[81]	1991	20	1‡	0·05	
Total		403§	15	0·04 (0·02, 0·06)	0·01 (0·01, 0·03)
Colostomy					
Londono-Schimmer *et al.*[72]	1994	289¶	5¶	0·02 (0·01, 0·04)	

Values in parentheses are 95 per cent confidence intervals. *All from cancer; †three from cancer; ‡7 months after operation, cause unspecified. §Excluding Hill (1999). ¶*n* = 289 calculated only for early postoperative mortality. n.c., Not calculable

Table 5 Overall morbidity rates

Reference	Year	*n*	Morbidity	Morbidity rate
Dynamic graciloplasty				
Altomare *et al.*[67]	1997	9	14	1·56
Baeten *et al.*[63]	1995	52	11	0·21
Baeten *et al.*[68]	2000	91	189	2·08
Cavina *et al.*[69]	1998	31	23	0·74
Geerdes *et al.*[70]	1997	20	7	0·35
Hill[71]	1999	n.c.*	n.c.	n.c.
Mander *et al.*[73]	1996	12	12	1·00
Mander *et al.*[74]	1999	64	87	1·36
Mercati *et al.*[75]	1991	7	1	0·14
Rosen *et al.*[76]	1998	28	14	0·50
Rouanet *et al.*[77]	1999	9	6	0·67
Rullier *et al.*[78]	2000	11	16	1·45
Violi *et al.*[80]	1999	13	7	0·54
Williams *et al.*[81]	1991	n.c.†	n.c.	n.c.
Total		347	387	1·12‡
Colostomy				
Londono-Schimmer *et al.*[72]	1994	203	104	0·51 (0·44, 0·58)

Values in parentheses are 95 per cent confidence intervals. *Pain only safety outcome measured. †Some patients included in Mander *et al.*[73] so not calculated here to avoid double counting. ‡95 per cent confidence interval not calculable. n.c., Not calculable

commonest complications for colostomy were paracolostomy hernia (21 per cent) and skin complications (12 per cent). Londono-Schimmer *et al.*[72] also relate that the cumulative risk of patients with a colostomy developing a paracolostomy hernia rose to 37 per cent at 10 years. Studies that reported on temporary or covering stomas (e.g. Baeten *et al.*[68]) were not included in this analysis because the stoma was not performed as the primary operation.

Table 6 All reported complications in primary studies

Complication	No. of events
Dynamic graciloplasty (*n* = 383)	
Infection	106 (28)
Stimulator and lead faults (including erosion, breakage, dislocation, displacement)	59 (15)
Leg pain	54 (13)*
Gracilis or colon injury (including ischaemia, injury, necrosis, perforation)	31 (8)
Battery exhaustion	29 (8)
Constipation	28 (7)
Anal pain	30 (7)*
Body pain	24 (6)
Stimulator-related pain	15 (4)
Neoanal stricture or stenosis	16 (4)
Deep vein thrombosis	6 (2)
Tendon displacement or detachment	9 (2)
Ineffective or non-contracting gracilis	6 (2)
Pulmonary embolism	2 (1)
Leg swelling, seroma or haematoma	3 (1)
Neuropraxia	2 (1)
Colonic fistula	3 (1)
Colostomy (*n* = 203)	
Paracolostomy hernia	43 (21)
Skin	24 (12)
Stoma prolapse	11 (5)
Stoma obstruction	11 (5)
Stoma stenosis	10 (5)
Retraction	3 (1)
Fistula	2 (1)

Values in parentheses are percentages. **n* = 428 for this complication

Efficacy

The efficacy of a procedure measures how effectively it achieves the technical goals that are not related to issues of safety. In the present context continence, reoperation rates and quality of life are considered.

Few probabilistic data were available for general measures of continence (*Table 7*), with only Baeten *et al.*[63] reporting statistically significant improvement following dynamic graciloplasty. Frequency of defaecation decreased from a mean of five times per day to twice a day, and time to delay defaecation increased from a mean of 0·15 to 19 min, at 12 months. No other primary study attempted a statistical test of these variables. The numbers of patients reported as achieving satisfactory continence ranged from 42 to 85 per cent. 'Satisfactory' continence was not defined consistently across studies, with criteria for success ranging from occasional episodes of incontinence to solids, to always continent to solids and liquids with episodes of incontinence to flatus. However, most studies defined a successful outcome as requiring at least continence to solids. Mavrantonis *et al.*[90] compared continence outcomes between groups in which the stimulator leads had been implanted either directly on to the nerve or intramuscularly; intramuscular implantation was significantly more likely to achieve satisfactory continence.

All primary studies contained anal manometry data (*Table 8*) and the majority reported a statistically significant improvement in anal sphincter pressure following dynamic graciloplasty. Mean preoperative basal anal sphincter pressure ranged from 28 to 38 mmHg (or from 15 to 40 cmH$_2$O for studies that used that measure). Mean postoperative stimulated anal sphincter pressure ranged from 56 to 95 mmHg (or from 36 to 105 cmH$_2$O).

All primary studies for which reoperation rates could be calculated reported multiple operations in at least some patients (*Table 9*), although the actual rates varied widely. Of those for which a definite figure could be calculated, the mean number of reoperations after graciloplasty was between 0·14 and 1·07 per patient. Similarly, all primary studies reported a need to explant the stimulator from at least some patients; the highest rate was 0·42 times per patient. Reoperation and stimulator explantation after dynamic graciloplasty were attributed to a wide range of causes, including perforation or erosion of the anal canal by the gracilis, perforation of the anal canal from enema, necrosis of the gracilis and/or the colon stump, detachment of the gracilis tendon from the ischial tuberosity, insufficient or excessive gracilis tension, stenosis of the anal canal, constipation, failure of the operation necessitating the creation of a stoma, lead or stimulator migration (or even expulsion from the body), infection of the leads or stimulator, battery failure, perineal abscess, perineal hernia, pain, development of rectocele and repair of fistula. Reoperation after colostomy was reported at 0·13 events per patient, with a cumulative figure at 11 years of 0·17. Reoperation after colostomy was needed because of paracolostomy hernia, stenosis, stoma prolapse, intestinal obstruction, retraction, fistula and peristomal suppuration.

No study directly compared quality of life outcome between dynamic graciloplasty and colostomy. Dynamic graciloplasty studies that did measure quality of life or psychosocial outcomes either compared successfully treated patients with unsuccessfully treated patients[63,68] (*Table 10*) or made no comparisons[71] (*Table 11*). Two reviews have examined quality of life following a colostomy but these only compared stoma with non-stoma (*Tables 12* and *13*)[66,79].

Unsurprisingly, in two studies by Baeten *et al.*[63,68] several quality of life measures were found to improve significantly following a successful dynamic graciloplasty compared with a failed operation; these included improvements in anxiety, task performance (effectiveness in one's occupation, ability to perform tasks around the home, personal relationships, sexual function and social life), social function, vitality and

Table 7 General measures of continence

Reference	Year	*n*	Percentage continent	Continence score*		Mean frequency of defaecation (per day)		Mean time to delay defaecation (min)		Mean enema retention time (s)	
				Preop.	Postop.	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.
Altomare *et al.*[67]	1997	5		16·4	5·4						
Baeten *et al.*[63]	1995	52	73§			5	4, 2‡‡, 2, 2‡‡, 2, 2	0·15	0·5, 11‡‡, –, 19‡‡, –, –		
Baeten *et al.*[68]	2000	72‡	63							0	75 (median)
Cavina *et al.*[69]	1998	31	85¶				0·6				
Geerdes *et al.*[70]	1997	15	53¶				3 (26 weeks)		11		
Mander *et al.*[73]	1996	12	42**								
Mander *et al.*[74]	1999	64	69††	19	6						
Mercati *et al.*[75]	1991	7							≥ 3–5		
Rosen *et al.*[76]	1998	28			2·6†						
Rouanet *et al.*[77]	1999	9	56††								
Rullier *et al.*[78]	2000	12	58								
Violi *et al.*[80]	1999	5		11	5						
Williams *et al.*[81]	1991	20	60††								

*Cleveland Clinic scores except †William's continence score. ‡Only patients without a stoma; continence achieved if more than 50 per cent reduction in incontinent episodes. §At least continent to all but flatus; ¶level I or II of William's continence score; **all at least occasionally incontinent to solid stool; ††continent to solids. For Baeten *et al.* (1995) postoperative values are for weeks 0, 8, 26, 52, 104 and 156. ‡‡P < 0·05 postoperative *versus* preoperative status (Wilcoxon signed rank test)

Table 8 Anal manometry

Reference	Year	*n*	Preoperative		Postoperative			
					Unstimulated		Stimulated	
			Basal (mmHg)	Squeeze (mmHg)	Basal (mmHg)	Squeeze (mmHg)	Basal (mmHg)	Squeeze (mmHg)
Altomare *et al.*[67]	1997	9	33(18)§		35(23)§		87(15)§	
Baeten *et al.*[63]	1995	52	38	50	42, 49, 50, 48, 52, 51†		61, 69, 75§§, 76§§, 77, 77†	
Baeten *et al.*[68]	2000	123	37(23)	58(34)¶	41(24) (n = 79)	81(41)¶ (n = 77)		
			38(23)¶	50(27)¶			58(31)¶ (n = 77)	93(39)¶ (n = 58)
Cavina *et al.*[69]	1998	31			38	105	56	147
Geerdes *et al.*[70]	1997	20			40(22)	92(33) (1 year)		
Mander *et al.*[73]	1996	12	15*		23*‡ (1 year)		36* (1 year)	76*‡ (1 year)
Mander *et al.*[74]	1999	64	40*	64*††	40*			117*††
Mercati *et al.*[75]	1991	7			12	70		
Rosen *et al.*[76]	1998	28	28§	39**	39** (1 year)	75** (1 year)		
Rouanet *et al.*[77]	1999	9			24(10)		95(25)	
Rullier *et al.*[78]	2000	15	30*		33*‡‡	200*	105*‡‡	
Violi *et al.*[80]	1999	13			33(11)	172(104)	70(22) (n = 5)	151(89) (n = 5)
Williams *et al.*[81]	1991	20	38	58	35		62	105

Values are mean(s.d.). *Pressures measured in cmH_2O. †Weeks 0, 8, 26, 52, 104 and 156. ‡P < 0·05 stimulated *versus* unstimulated (Wilcoxon signed rank test); §P < 0·01 stimulated *versus* others (Wilcoxon signed rank test); ¶P < 0·001 postoperative *versus* preoperative (paired t test); **P < 0·01 postoperative *versus* preoperative (one way analysis of variance); ††P < 0·05 postoperative *versus* preoperative (Wilcoxon rank sum test); ‡‡P < 0·01 stimulated *versus* unstimulated (Mann–Whitney U test); §§P = 0·001 postoperative *versus* preoperative (Wilcoxon signed rank test)

role physical. There were no significant improvements reported in general health, body pain, role emotional, physical function, mental health or a general quality of life measure (although the last two approached statistical significance).

The results from a review by Sprangers *et al.*[79] of multiple studies comparing quality of life measures for stoma *versus* non-stoma were, with two exceptions, uniform. Non-stoma scored significantly higher on a broad range of measures, including fewer bowel-related problems, improved

Table 9 Reoperation rates

Reference	Year	*n*	Risk of reoperation	Stimulators removed
Dynamic graciloplasty				
Altomare *et al.*[67]	1997	9	1·0	33%
Baeten *et al.*[63]	1995	52	At least 0·13	13%
Baeten *et al.*[68]	2000	123	0·86	At least 2%
Cavina *et al.*[69]	1998	31	0·74	19%
Geerdes *et al.*[70]	1997	20	At least 0·25	n.c.
Mander *et al.*[73]	1996	12	0·67	17%
Mander *et al.*[74]	1999	64	n.c.	At least 42% (all battery failures)
Mercati *et al.*[75]	1991	7	0·14	Not applicable
Rosen *et al.*[76]	1998	28	0·32	18%
Rouanet *et al.*[77]	1999	9	0·33	n.c.
Rullier *et al.*[78]	2000	15	1·07	At least 13%
Violi *et al.*[80]	1999	13	0·38	20% (1 battery failure of 5 implants)
Williams *et al.*[81]	1991	20	n.c.	n.c.
Colostomy				
Londono-Schimmer *et al.*[72]	1994	203	0·13 (cumulative 0·17 at 11 years)	

n.c., Not calculable

Table 10 Quality of life measures for dynamic graciloplasty – Baeten *et al.*[63,68]

	Treatment failure	Treatment success	*P*
Baeten *et al.* (1995)[63]*			
Anxiety	5	−6	0·002
Depression	7	−2	
Task performance	−1	−2	0·01
Baeten *et al.* (2000)[68]†			
Mental health	59	68	0·08
Role emotion	49	64	0·14
Social function	53	68	0·02
Vitality	43	53	0·04
General health	56	61	0·30
Body pain	49	51	0·26
Role physical	38	61	0·03
Physical function	64	70	0·36

*Median change at 12 months; negative score indicates improvement, positive indicates worsening (Wilcoxon signed rank test). †Short Form 36 scores; additionally, Zung depression and State-Trait Anxiety Inventory anxiety scales were within normal range throughout study. Quality of life measured on a visual analogue scale 1 scale was 5·2 before operation and 5·8 afterwards ($P = 0·06$) (paired *t* test)

Table 11 Quality of life measures for dynamic graciloplasty – Hill[71]

Emotional function		Social function		Current health		Body pain		Satisfaction with graciloplasty		Overall life satisfaction	
High	24	High	28	Excellent	4	None	21	High	23	Excellent	13
Good	2	Medium	13	Very good	14	Mild	9	Medium	10	Very good	11
Medium	1	Low	4	Good	12	Moderate	9	Low	11	Good	10
Low	7			Fair	8	Severe	5			Fair	3
				Poor	7	Severe+	1			Poor	8

Values are number of patients sorted by Short Form 36 scores, except for satisfaction scales

Table 12 Quality of life measures for colostomy – Sprangers *et al.*[79]

	Stoma		No stoma	
	n	Percentage of patients	*n*	Percentage of patients
Physical functioning				
< 3 bowel movements/day	29	62	31	23
Flatus/gas problems	303	49–50	195	15–37
Constipation	265	13	155	23
Use of bowel stabilizing drug	30	13	36	44
Use of bowel stabilizing drug	38	60	40	30
Urinary problems	265	24	155	12
3–5 diet restrictions	38	42	40	15
Odour problems	38	63	40	20
Psychological functioning				
Depression	214	22–50	110	7–43
Depression	38	32	40	10
Loneliness	214	27	110	12
Suicidal ideation	214	10	110	3–4
Feelings of stigma	265	26–54	155	13–41
Low self-esteem	265	43	155	27
Concern for appearance	265	20	155	9
Change in body image	38	66	40	5
Social functioning				
Return to work	15	40	18	83
Worsening partner relation	265	29	155	14
Visit friends less	114	27	110	17
Visit cinema less	114	61	110	42
Decrease in leisure pursuits	38	50	40	18
Less participation in activities	265	63	155	49
Leave home < 1/week	265	18	155	8
Less interest in social activity	265	43	155	31
Sexual functioning				
Sexual dysfunction	18	67	20	30
Total erectile impotence	20	50	40	5–20
Ejaculatory impotence	20	70	40	25–40
Incapable of penetration	20	55	40	10
Less frequent intercourse	20	60	40	5–25

Only significant results shown ($P < 0{\cdot}05$ stoma *versus* no stoma)

Table 13 Quality of life measures for colostomy – Grumann *et al.*[66]

	Main effect on time (A0, A1, A2)*	Main effect on group (APR *versus* AR)†	Time by group interaction*
Role function	A0 > A1, $P = 0{\cdot}02$		AR > APR at A0, A1 AR < APR at A2
Emotional function	A0 < A1, $P < 0{\cdot}01$ A1 < A2, $P < 0{\cdot}05$		
Sleeplessness		AR > APR, $P = 0{\cdot}03$	
Constipation		AR > APR, $P < 0{\cdot}01$	
Diarrhoea		AR > APR, $P < 0{\cdot}01$	
Body image	A1 > A2, $P = 0{\cdot}03$		
Future perspective	A0 < A1, $P < 0{\cdot}01$ A1 < A2, $P < 0{\cdot}01$		
Micturition problems	A0 < A1, $P = 0{\cdot}04$		

Only significant results shown (multivariate analysis of variance). *High score denotes low distress/good function; †high score denotes high level of distress. A0, before operation; A1, 6–9 months after operation; A2, 12–15 months after operation. APR, abdominoperineal resection; AR, anterior resection psychological functioning (including lower rates of depression, suicidal ideation and loneliness), improved social functioning (with 83 per cent returning to work compared with 40 per cent), and lower rates of sexual dysfunction, at least among men (*Table 12*). The two exceptions were 'constipation', for which patients with a stoma reported significantly fewer problems, and 'use of bowel stabilizing drugs', for which the results from two studies were contradictory.

A recent study by Grumann *et al.*[66] of 73 patients treated with either abdominoperineal resection or anterior resection reported similar results wherein the latter operation was associated with significantly increased problems with constipation and diarrhoea. Conversely, this study found significantly greater problems in the anterior resection group for sleeplessness as well as significantly worse 'role function' at 12–15 months after operation. The study also reported a trend for patients with anterior resection to score lower on a variety of quality of life measures, although none of these differences was statistically significant. Patients with an anastomosis within 5 cm of the anal verge tended to score lower than those with a higher anastomosis.

Animal studies

Two animal studies were found suitable for inclusion in the review. Rosen *et al.*[101] used sartorius muscles on excluded small bowel segments in dogs to simulate and compare two variants of the graciloplasty: the alpha loop and the split sling (in which the muscle is looped back through an incision in itself). The sartorius muscle was used because of its similarity to the human gracilis (the dog gracilis is a flat, wide muscle unsuitable for looping around the colon). There was no significant difference in either resting or contraction pressures between these two variants. Geerdes *et al.*[102] transposed the gracilis muscles of giant Flemish rabbits around plastic tubes to assess the effects of vascular delay and delayed stimulation on contraction pressures and muscle fatigue. No significant differences were found in contraction pressures between groups that began stimulation 3 days and 6 weeks after operation, or in which vascular delay was performed 5 weeks before operation and stimulation begun 3 days after operation. However, delay in stimulation training resulted in significantly greater fatigue resistance in the transposed muscle.

Cost-effectiveness

Only one study addressed the cost-effectiveness of dynamic graciloplasty compared with colostomy, calculating the total incremental cost of dynamic graciloplasty as US $13 221 compared with US $53 065 for colostomy[83]. However, this work has been criticized on several of its assumptions, including an overly optimistic lifetime failure rate for stimulators of only 2 per cent, assumed costs of treating complications and a very high rate of colostomy pouch replacement (see Madoff's discussion to Reference 83). With regard to this last point, Madoff points out that the study's Dutch authors assumed twice-daily pouch changes (at US $5 each) whereas his own experience was that patients in the USA change their pouch twice a week. The difference in overall costs produced by this alternative analysis was marked: the study's authors calculated annual colostomy pouch costs at US $4393 compared with Madoff's estimate of US $553 (plus ancillary supplies).

Discussion

It seems safe to conclude that the mortality rate for both dynamic graciloplasty and colostomy is about 2 per cent. When operative morbidity is considered, compelling differences appear, although they are non-probabilistic. That the technically demanding dynamic graciloplasty has a high morbidity rate in excess of one event per patient is perhaps not as surprising as that the comparator, colostomy, should also be associated with an overall morbidity figure of 0·5 per patient, even in the hands of experienced colorectal surgeons. Colostomy is not a new operation and Londono-Schimmer *et al.*[72] make the point that perhaps it is time to question some of the tenets currently accepted in good stomal surgery. These authors argue, in particular, that siting the stoma through the belly of the rectus abdominis muscle to prevent herniation does not appear to be justified and that an extraperitoneal approach, where possible, results in a significantly lower rate of parastomal herniation.

While dynamic graciloplasty appears to have a higher rate of complications, some of which are serious, there is the possibility that as the technique evolves these rates may decline. In particular, it is possible that a more durable stimulator with more reliable batteries will lead to fewer failures and reoperations. Likewise, improved techniques may lead to reduced erosive and ischaemic injuries to either or both the transposed gracilis and the neoanus. Such potential developments hold out the hope of more successful graciloplasty, with sufficient tension to act as an effective neosphincter. It is similarly possible that inspired improvements in stoma surgery may improve the safety of colostomy.

As an effective treatment for intractable incontinence, the successful dynamic graciloplasty is clearly superior to the colostomy, which is completely incapable of allowing the patient to determine when and where voiding will occur. Unfortunately, the rate of failure of dynamic graciloplasty is high, with a satsifactory degree of continence being achieved in only 42–85 per cent of patients, and most studies reporting success rates of 60 per cent or less. As the result of an unsuccessful graciloplasty is usually conversion to a stoma, it is important to ask whether the risks of morbidity and reoperation in dynamic graciloplasty outweigh the benefit of successful outcome.

Cost-effectiveness data are insufficient and too contentious to be useful. For the present the core question seems to revolve around quality of life issues. Patients with a stoma are significantly more likely to report poorer outcomes on a raft of quality of life measurements than patients without a stoma. The same is true for those who undergo unsuccessful dynamic graciloplasty compared with those for whom the operation is a success.

Dynamic graciloplasty is a complex operation with a less than assured outcome. However, that such a difficult surgical technique has been developed is some indication of the distress that patients with intractable faecal incontinence suffer, and also of the shortcomings of the principal alternative, the current 'gold standard' of colostomy. The decline in quality of life subsequent to the creation of a stoma still makes graciloplasty an attractive option, despite its drawbacks, for some individuals.

The ASERNIP-S Review Group allocated the following safety and efficacy classification for dynamic graciloplasty for the treatment of faecal incontinence. *The safety of the procedure cannot be determined at the present time due to an incomplete and/or poor-quality evidence base. It is recommended that further research be conducted to establish safety.* Specifically, since the procedure appears to carry a higher morbidity rate than colostomy and owing to the technical demands of dynamic graciloplasty, it is recommended that this procedure is performed only in centres where it is done routinely. It is further advised that patients must be informed of the probability that the treatment may have to be converted to colostomy at some time in the future if serious morbidity results. The actual relative risk of morbidity that dynamic graciloplasty presents in comparison to colostomy remains undetermined and should be assessed by a non-randomized controlled clinical trial, as randomization may prove impossible for ethical or practical reasons. Since quality of life outcomes likewise remain undetermined, these measures should also be included in any such comparative trial.

Efficacy is established. Dynamic graciloplasty is equal to, or better than, the best practice based on the currently available evidence. The procedure may be introduced into practice. Specifically, although dynamic graciloplasty appears to be an efficacious alternative to colostomy for restoring continence in around 60 per cent of patients (including those who have had congenital disorders of the anorectum), it is recommended that patients be well informed of the probability of failure of this operation.

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Randomized clinical trial of Ligasure™ *versus* open haemorrhoidectomy

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Background: Postoperative pain associated with open haemorrhoidectomy remains problematic. Haemorrhoidectomy performed using bloodless bipolar diathermy – Ligasure™ – may have advantages over conventional open haemorrhoidectomy in terms of operating time and postoperative pain.
Methods: Thirty-four patients were randomized to undergo Ligasure™ (18 patients) or diathermy (16) haemorrhoidectomy. The operating time, amount of pain and postoperative analgesic requirement, postoperative complications and overall patient satisfaction were documented.
Results: The median duration of operation was shorter in the Ligasure™ haemorrhoidectomy group (5·1 *versus* 9·2 min; $P < 0{\cdot}001$). There was no statistically significant difference in the postoperative pain score, but the median analgesic requirement was lower in the Ligasure™ group (850 *versus* 1600 mg tramadol; $P = 0{\cdot}013$). Patient satisfaction was similar in both groups.
Conclusion: Ligasure™ haemorrhoidectomy is quick and bloodless and, although as painful as diathermy haemorrhoidectomy, is associated with a reduced analgesic requirement.

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Introduction

Haemorrhoidectomy is the most effective cure for prolapsing haemorrhoids[1]; however, it is associated with considerable postoperative pain. The attempts to reduce pain following haemorrhoidectomy have included alterations in surgical technique and modifications in perioperative treatment regimens. Although some surgeons have altered their practice, the evidence for the benefits of antibiotics and laxatives has not gained universal acceptance[2]. Haemorrhoidectomy using diathermy excision has been shown to be associated with less bleeding, a shorter operating time and a lower postoperative analgesic requirement, but the technique is not intrinsically less painful than conventional haemorrhoidectomy[3]. Stapled haemorrhoidectomy has been widely adopted and, although recent results with this technique are encouraging[4], the findings are far from conclusive.

Ligasure™ (Valleylab, Boulder, Colorado, USA) is a new haemostatic device designed primarily for use in abdominal surgery. The device seals blood vessels of up to 7 mm in diameter using a precise amount of bipolar energy and pressure that permanently changes collagen and elastin within the vessel wall. Haemorrhoidectomy performed using Ligasure™ is entirely bloodless, easy to learn and does not require the specialist skills required for the stapled anoplasty. In the present study haemorrhoidectomy using Ligasure™ was compared with open haemorrhoidectomy performed by means of diathermy excision.

Patients and methods

Local ethics committee approval was obtained. Appropriate informed written consent was obtained from patients admitted for haemorrhoidectomy for symptomatic prolapsing haemorrhoids who required a three-quadrant haemorrhoidectomy. Randomization was performed at the time of anaesthesia by randomization using sealed envelopes. Sixteen patients underwent a standard diathermy haemorrhoidectomy and 18 had a Ligasure™ haemorrhoidectomy. The patients were blinded to the treatment that they were to undergo. After operation the patients were kept unaware of what procedure had been performed until the consignment of the research data in the outpatient department 2 weeks after operation. Patients taking anticoagulants, those undergoing simultaneous procedures and those previously operated on for haemorrhoids were excluded from the study.

All procedures were performed under general anaesthesia by either a consultant (15 patients) or a higher surgical trainee (19). The operation was carried out with the patient in the lithotomy position. The standard haemorrhoidectomy was performed using a Parks' self-retaining retractor. Adrenaline 1 : 200 000 without local anaesthetic was infiltrated to aid haemostasis and to help define the planes of dissection. Cutting diathermy dissection encompassing the haemorrhoid was performed. Haemostasis was secured with forceps coagulating diathermy. On completion an absorbable haemostatic pack was placed in the anal canal.

The Ligasure^{TM} procedure was performed using a Ferguson retractor. The haemorrhoidal tissue was grasped in an artery clip and brought towards the lumen of the anal canal. The medium-sized Ligasure^{TM} device was applied across the base of the haemorrhoidal complex (*Fig. 1*). The coagulation foot pedal was pressed until a characteristic two-tone sound from the machine confirmed complete coagulation of the tissue. The feedback-controlled response system delivers the appropriate amount of energy required to seal the tissue and the flow of current is automatically halted to prevent further coagulation. The coagulated strip was then cut (*Fig. 2*) and the haemorrhoid removed. No further haemostasis or dressing was required. An independent observer timed the operations.

The perioperative medical treatment was standardized. Patients were given 10 ml lactulose (twice daily from the day before operation), metronidazole (400 mg three times daily) and 0·2 per cent glyceryl trinitrate paste (hospital pharmacy, Princess Alexandra Hospital), applied twice daily, for a total of 5 days after the operation. Tramadol hydrochloride, an opiate analgesic with less tendency to constipate, was prescribed (50 mg as required, up to a maximum of 100 mg 4 hourly and 400 mg daily). Patients were asked to document the amount of analgesia required and the pain experienced at the time of waking on each postoperative day for 7 consecutive days using a visual analogue scale. From this a weekly median score was calculated[5].

All patients were admitted to hospital for surgery and were discharged the following day, although four patients from the Ligasure^{TM} group requested discharge on the day of operation. Outpatient follow-up was undertaken at 2 weeks when the wound was inspected, and at 6 weeks a digital rectal examination was performed.

It was considered that a reduction in pain of 50 per cent and in operating time of more than 30 per cent would be

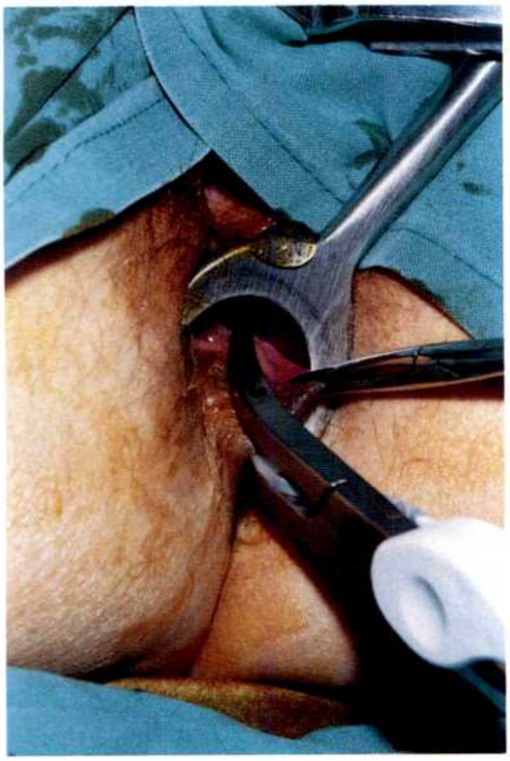

Fig. 1 Ligasure^{TM} device applied across the base of the haemorrhoid to be excised

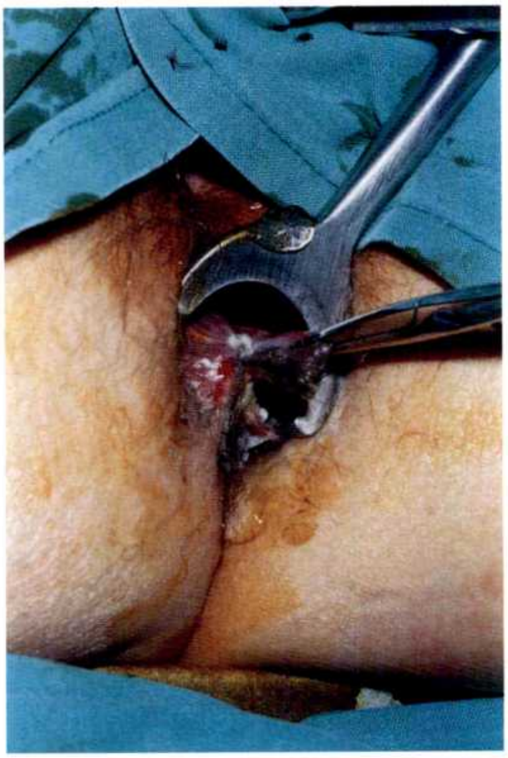

Fig. 2 A coagulated strip of tissue is divided

clinically relevant, and these were chosen as parameters with which to calculate the study power. Initial power calculations suggested that a minimum of 28 patients would be required to achieve statistical significance with a power of 80 per cent at the 5 per cent significance level. However, it rapidly became apparent that postoperative pain variability was such that statistical difference, if present, would be achieved only with the recruitment of a prohibitively large sample size.

Using a value of less than 0·05 as significant, the Mann–Whitney *U* test was used to establish the difference between open and Ligasure$^{\text{TM}}$ haemorrhoidectomy with respect to the duration of operation, postoperative pain and analgesic requirement. Fisher's exact test was used to assess the significance in the incidence of complications in the two groups. Results are expressed as median (range) unless otherwise stated.

Results

Thirty-four patients were admitted to the trial. There were six men and ten women of mean age 49 (range 30–73) years in the open haemorrhoidectomy group, and six men and 12 women of mean age 44 (range 33–58) years in the Ligasure$^{\text{TM}}$ haemorrhoidectomy group.

The median duration of operation was 5·1 (2–9) min for Ligasure$^{\text{TM}}$ haemorrhoidectomy and 9·2 (7·6–14·1) min for open haemorrhoidectomy ($P < 0{\cdot}001$) (*Fig. 3*). The median postoperative pain score was 5·2 (2–8) in the Ligasure$^{\text{TM}}$ group and 4·6 (1–8·4) in the open haemorrhoidectomy group ($P = 0{\cdot}28$) (*Fig. 4*). The median total 7-day analgesic requirement was 850 (0–2750) mg tramadol in the Ligasure$^{\text{TM}}$ group and 1600 (0–2100) mg in the open haemorrhoidectomy group ($P = 0{\cdot}013$).

There were three complications in the open haemorrhoidectomy group and none in the Ligasure$^{\text{TM}}$ group. The three complications were one episode of reactive bleeding requiring a blood transfusion on the day after operation, one episode of secondary bleeding on day 5 and one readmission for postoperative urinary retention on day 3. At the 6-week follow-up no anal stenosis or loss of anal tone was identified and no incontinence of flatus or liquid was reported in either group.

There was no difference in overall satisfaction between the two groups of patients.

Discussion

Haemorrhoidectomy is the procedure that cures prolapsing haemorrhoids most effectively[1]. The widely performed excision–ligation procedure first described by Milligan and Morgan[6] can be bloody and is associated with troublesome postoperative pain. Many alterations in surgical technique and perioperative care have been suggested but few have produced sufficient evidence to change clinical practice. Use of preoperative lactulose and metronidazole reduces perioperative pain[7,8] and has recently been included in evidence-based guidelines for the practice of haemorrhoidectomy[9]. Despite its advocates, of the approximately 50 000 stapled anoplasty procedures performed to date in Europe and Asia[10] very few had until recently been a part of a randomized controlled trial. The trials that have been performed do suggest that the procedure is associated with a good outcome, less postoperative pain and an earlier return to work[4,11,13]. However, in one trial[4] ligation of the haemorrhoidal pedicle, thought to be associated with increased postoperative pain, was performed in the control

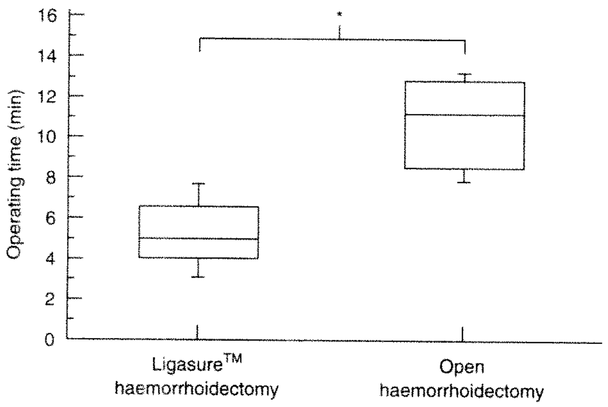

Fig. 3 Median operating times for Ligasure$^{\text{TM}}$ and open haemorrhoidectomy. Boxes denote the range. $^*P < 0{\cdot}001$ (Mann–Whitney *U* test)

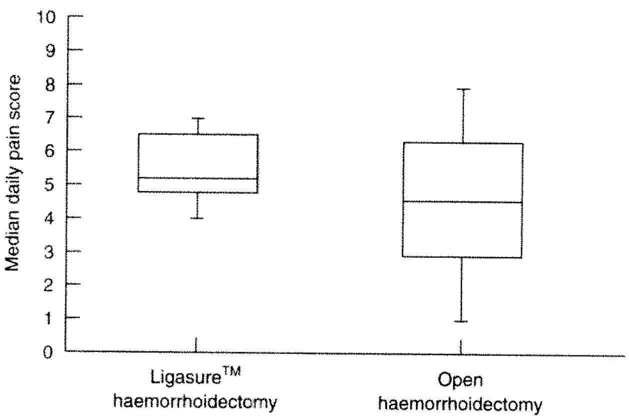

Fig. 4 Comparison of median daily pain score following Ligasure$^{\text{TM}}$ and open haemorrhoidectomy. Boxes denote the range

group. There have also been less favourable reports involving complications such as chronic anal pain and faecal urgency[10], rectovaginal fistula[2] and pelvic sepsis[14] following stapled anoplasty. It remains to be seen whether stapled anoplasty becomes the treatment of choice for third-degree haemorrhoids.

Diathermy haemorrhoidectomy is a widely used technique and, although not conclusively associated with less pain, appears to be associated with a lower analgesic requirement[3]. According to the same authors it is also preferable because of the shortened operating time. Improved haemostasis may also offer better visibility and therefore a more accurate dissection. The reduced operating time associated with electrocautery dissection is related to better haemostatic control and lack of any need to ligate the pedicles. The absolute bloodlessness, characteristic of the Ligasure™ haemorrhoidectomy, takes this a step further. The absence of blood in the operative field is such that no time is required to secure haemostasis, and as a consequence the mean operating time in this study was halved.

As in other randomized trials that have assessed the value of diathermy, laser, open and closed haemorrhoidectomy[9], this study has failed to demonstrate any reduction in postoperative pain. However, the mean postoperative analgesic requirement following the Ligasure™ haemorrhoidectomy was lower than that of diathermy haemorrhoidectomy, and some patients in the Ligasure™ group wished to be discharged on the day of operation. However, the pain on the day of operation itself was not measured, so the request of some patients to be discharged in the afternoon following morning surgery should be interpreted with caution.

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Original article

Long-term results of bilateral thoracoscopic splanchnicectomy in patients with chronic pancreatitis

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Background: The management of pain in patients with chronic pancreatitis is difficult. The aim of this prospective study was to evaluate the early and long-term pain relief provided by bilateral thoracoscopic splanchnicectomy.

Methods: From August 1995 to August 1999, 44 patients with chronic pancreatitis underwent bilateral thoracoscopic splanchnicectomy. Data were collected prospectively. Thirty-six patients required opioids. Pain intensity was registered before operation and at regular intervals after surgery by means of a visual analogue scale (VAS). Use of analgesics (opioids; non-steroidal anti-inflammatory drugs and acetaminophen; no analgesics or aminocetophen) was noted before and after splanchnicectomy. Median follow-up was 36 (range 12–60) months.

Results: The procedure was technically successful in 40 patients. Thirty-six patients had no complications. Eleven of 24 patients who have been followed up for 24 months or more had a significantly reduced VAS score at 2 years (median (range) 8·5 (7–10) *versus* 2·5 (0–5); $P < 0{\cdot}01$). The cumulative rate of pain relief was 46 per cent 48 months after splanchnicectomy.

Conclusion: Bilateral thoracoscopic splanchnicectomy alleviated pain in patients with chronic pancreatitis. It was associated with a low morbidity rate and no deaths. Pain eventually recurred in approximately 50 per cent.

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Introduction

Pain in patients with chronic pancreatitis is a challenging problem for surgeons and gastroenterologists. The main goal of treatment is to provide sufficient and lasting pain relief without the use of opioids and deterioration of pancreatic function. Surgical as well as non-operative approaches have been advocated to treat pain in these patients. The basis for prolonged conservative treatment is the assumption that chronic pancreatitis ultimately leads to complete fibrosis and that patients will become pain free[1,2]. However, 50 per cent of patients with chronic pancreatitis appear to suffer from relapsing pain attacks up to 10 years of observation. Moreover, 30–50 per cent of patients do not respond to conservative treatment and become dependent on opioids[3].

Surgery for pain relief comprises drainage and resection procedures. The choice between these procedures depends essentially either on the diameter of the main pancreatic duct and duct abnormalities or the presence of an inflammatory mass in the head of the pancreas. Both types of operation result in long-term pain relief in about 60–80 per cent of patients, but they involve considerable morbidity and mortality[4–8] and are therefore carried out with reluctance.

Thoracoscopic bilateral splanchnicectomy is an operative technique that has been introduced recently to alleviate pain irrespective of the type of anatomic abnormality. Using a minimally invasive approach, nociceptive fibres originating from the pancreatic area, incorporated in the splanchnic nerves, are transected at the thoracic level where they enter the paravertebral sympathetic chain. This technique seems to fulfil the therapeutic purpose of sufficient pain relief with low morbidity and mortality rates, and without deterioration of pancreatic function[9–11]. Early results are promising, but only one prospective study with a follow-up longer than 1 year has been reported[12]. This was a prospective study of the early and long-term effects of bilateral thoracoscopic splanchnicectomy on pain relief and complications in a large unselected group of patients with continuous pain from chronic pancreatitis.

Patients and methods

From August 1995 to December 1999, 44 patients underwent bilateral thoracoscopic splanchnicectomy (26 men and 18 women). Mean age was 41 (range 15–63) years. All patients had chronic pancreatitis, diagnosed by means of endoscopic retrograde cholangiopancreatography, computed tomography (CT) and/or magnetic resonance cholangiopancreatography, according to standard criteria[13]. The presence of pseudocysts was ruled out. Twenty-one of the 44 patients neither had a dilated main pancreatic duct nor an inflammatory mass in the head of the pancreas. Four patients had a dilated duct (4 mm or more) and five patients had an enlarged pancreatic head on CT. Previous pancreatic surgery rendered accurate radiological interpretation of the pancreatic abnormalities difficult in the remaining 14 patients.

Twenty-eight patients had undergone one or more surgical or endoscopic interventions for pain. Five patients had previously undergone a Beger resection and three patients a Partington–Rochelle procedure. Nine patients had had a resection. In eight patients the pancreatic duct had been drained endoscopically with a stent. Papilloplasty, biliodigestive bypass and pseudocyst drainage had been performed in three, two and three patients respectively. Two patients had undergone neurolytic coeliac blockade unsuccessfully.

The median interval between the onset of pancreatitis and operation was 4·6 (range 1·4–14·8) years. In 24 patients alcohol abuse was considered to be the cause of the pancreatitis. Four patients had hereditary pancreatitis, four patients had a pancreas divisum and in two pancreatitis developed after trauma. In the remaining ten patients the cause of chronic pancreatitis was unknown. Thirty-four patients were referred from other hospitals. Twelve patients were (partly) at work before operation. The remaining 32 patients were unable to work, on social welfare or capable of doing only light housekeeping mainly because of pancreatic disease.

Data on pain and pain medication were collected prospectively during regular outpatient visits before and after splanchnicectomy. Pain was scored by means of a visual analogue scale (VAS; zero represented no pain and 10 intractable pain) for 1 week at 3-month intervals during the first 24 months and at 6-month intervals thereafter. Use of medication was noted and divided into three groups: no medication or acetaminophen, acetaminophen and/or non-steroidal anti-inflammatory drugs (NSAIDs), and opioids with or without NSAIDs. Failure of treatment was defined as persistence of pain needing additional therapy after the procedure or recurrence of pain necessitating the same or increased amounts of analgesic compared with that before operation.

The surgical procedure has been described previously[11]. Nerves were transected electrosurgically in the first 22 patients. Thereafter, patients were treated with a harmonic scalpel (Ultra-Cision®; Johnson & Johnson Medical, Amersfoort, The Netherlands). Postoperative pain was managed routinely by parenteral administration of opioids, usually intravenous morphine via a patient-controlled analgesia (PCA) device. Gradual tapering of the opioids used before operation was therefore accomplished, leaving the patient in partial control of the pain with the PCA.

Statistical analysis

Pain scores were compared with a Wilcoxon signed rank sum test. Differences were considered statistically significant when $P < 0{\cdot}05$. Pain relief was analysed by the life-table method. Endpoints of follow-up were failure of treatment, death and end of the observation period.

Results

The median follow-up was 36 (range 12–60) months. Twenty-four patients were followed up for 24 months or more. The median preoperative VAS score was 8·5 (range 7–10). Thirty-six patients required opioids. Median duration of opioid use was 38 months, varying from 6 to 84 months.

Early and late complications

Splanchnicectomy was technically successful in 40 patients. Four patients had severe pleural adhesions on one or both sides owing to existing pulmonary complications after necrotizing pancreatitis or after surgery for chronic pancreatitis. After adhesiolysis, the splanchnic nerves were difficult to visualize and complete denervation was uncertain. Transient pain lasting for 1–3 days related to trocar insertion was experienced by almost all patients. Three patients had intercostal neuralgia persisting for a longer period of time. This was managed successfully by carbamezapine. One patient stayed for 2 days in the intensive care unit because of respiratory failure caused by preoperative aspiration. No patient died.

Minor complications were encountered in four patients. In two a pneumothorax required drainage. One patient had a wound infection and one a pneumonia. Thirty-six patients had no complications. Median hospital stay was 4 (range 1–10) days.

Early pain relief

Pain scores at 6 months after surgery were significantly lower than preoperative values ($P < 0.01$). Early results at 6 months are shown in *Fig. 1*. Pain medication at 6 months is listed in *Table 1*. Pain persisted or recurred within 6 months in 11 patients and between 6 and 12 months in another six. In all four patients with a technically unsuccessful procedure pain recurred within 6 months.

Long-term pain relief

There were five patients with long-term failure at 15, 15, 18, 36 and 48 months after splanchnicectomy. Eleven of the 24 patients who have been monitored for 2 years or more had a significantly reduced VAS score (median (range) 8·5 (7–10) *versus* 2·5 (0–5); $P < 0.01$). One patient died from a gastric carcinoma 1 year after splanchnicectomy. This patient had only mild epigastric discomfort at 9-month follow-up compared with severe abdominal pain before operation. There was no difference in failure rate between the nine patients with a dilated duct or an inflammatory mass in comparison to 21 patients without these features.

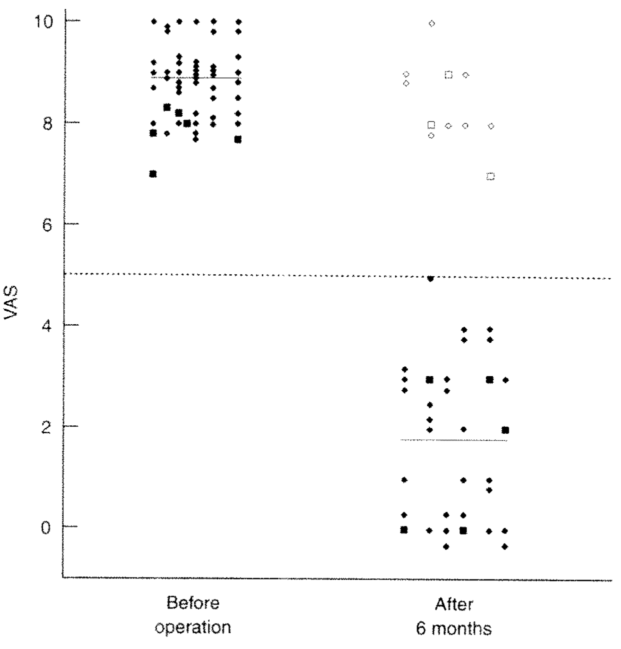

Fig. 1 Scattergram showing visual analogue scale (VAS) scores before and 6 months after bilateral thoracoscopic splanchnicectomy. Circles represent patients with opioid use and squares represent patients on non-steroidal anti-inflammatory drugs before splanchnicectomy. Open circles and squares represent patients in whom splanchnicectomy failed

Pain medication at a median follow-up of 36 months is listed in *Table 1*. In *Fig. 2* the cumulative probability of pain reduction after splanchnicectomy is depicted. Most failures occurred within the first year. The probability of pain relief 4 years after splanchnicectomy was 46 per cent.

Discussion

This report describes the pain-relieving effect of bilateral thoracoscopic splanchnicectomy in patients with chronic pancreatitis. This minimally invasive procedure resulted in early pain relief in the majority of patients, with a mortality rate of zero, a low complication rate and a short hospital stay. Pain, however, recurred in about half of the patients in the long term.

The management of pain in these patients before the splanchnicectomy was difficult, as reflected by the high percentage of opioid use, the long history of pain and the significant number of failed previous operative and anaesthetic procedures. Initially thoracoscopic splanchnicectomy may have been perceived by patients and specialists as a 'salvage' procedure but, encouraged by the preliminary excellent results, the procedure became first choice as surgical intervention[11]. This alternative surgical approach did not influence early and late relapse of pain. Patients with a dilated main pancreatic duct or an inflammatory mass in the pancreatic head in particular, who were good candidates for either a drainage procedure or a duodenum-preserving resection of the pancreas, did not have a worse outcome after splanchnicectomy than patients without these findings.

The procedure aimed at complete splanchnic nerve transection with the least operative morbidity for the patient. Unlike other authors[12,14], in this study the parietal pleura was routinely opened from the fifth to the 12th thoracic vertebral level, transecting all fatty tissue between the pleura and the intercostal vessels containing the main splanchnic trunks and their branches, thus assuring complete denervation. The vaporizing effect and low heat of the harmonic scalpel helped to meticulously dissect the subpleural tissue, leaving the vasculature uninjured, and maintaining visibility. Severe bleeding needing thoracotomy, as reported by Ihse *et al.*[12] using electrocautery, was not encountered. Patients in whom technical difficulties were encountered and complete denervation was uncertain continued in pain or had pain recurrence within 6 months, suggesting a correlation between technical success and pain relief. Seemingly in contrast, no correlation was found between the number of cut nerves and the degree of pain relief in a recent series of 21 patients with chronic

Table 1 Pain medication before and at 6 months after bilateral thoracoscopic splanchnicectomy, and at the end of follow-up

			End of follow-up*	
	Before (*n* = 44)	6 months (*n* = 44)	Failures (*n* = 22)	Non-failures (*n* = 22)
Opioids	36	12	19	1
NSAIDs and acetaminophen	8	10	3	6
No analgesics or acetaminophen	0	22	0	15

*Median follow-up 36 months. NSAIDs, non-steroidal anti-inflammatory drugs

Table 2 Review of reported series of thoracoscopic splanchnicectomy

Reference	Year	*n*	Uni/bilateral	Opioid use	Success rate (%)	Median follow-up (months)
Cushieri *et al.*[15]	1994	5	0/5	5 of 5	60	8
Maher *et al.*[14]	1996	15	9/6	11 of 15	79	18
Kusano *et al.*[10]	1997	9	6/3	n.s.	78	14
Andrén-Sandberg *et al.*[9]	1995	13	0/13	n.s.	100	9
Buscher *et al.*[11]	1999	26	0/26	21 of 26	58	14
Ihse *et al.*[12]	1999	21	0/21	14 of 21	75	42
Present study	2001	44	0/44	36 of 44	46	36

n.s., Not stated

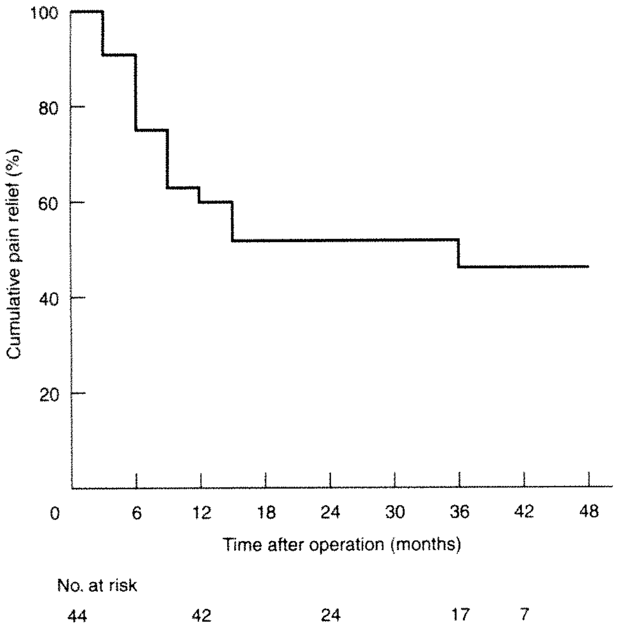

Fig. 2 Cumulative rate of pain relief after bilateral thoracoscopic splanchnicectomy

pancreatitis undergoing bilateral thoracoscopic splanchnicectomy[12].

These early results are in agreement with those of others, who have reported 60–80 per cent pain relief after 6 months (*Table 2*). The varying percentages are probably explained by differences in interpreting pain relief and in defining 'failure'. During follow-up half of the present patients had recurrence of pain and were back on their initial daily dose of analgesics or even more. There may be several explanations for pain recurrence. First, other sensory nerves that run from the pancreas to the semilunar ganglion and subsequently in the splanchnic nerves can take over nociceptive transmission of pancreatic impulses. The parasympathetic innervation by the vagus may carry such pain signals from the pancreas. Based on this assumption, some authors advocate a vagotomy in addition to a splanchnicectomy[16,17]. The benefit of an additional vagotomy, however, has not been adequately demonstrated. Second, pain recurrence is related to altered nociceptive sensory receptor function in and around the pancreas. There are two distinctive classes of nociceptors innervating internal organs: the high-threshold receptors, whose nerve activity is entirely evoked by noxious stimuli, and the low-threshold receptors, which have a range of stimulation intensity, from innocuous to noxious. Receptors that were unresponsive to certain stimuli may theoretically become activated. In the presence of inflammation, for example, so-called silent nociceptors are activated and contribute to the perception of chronic visceral pain[18,19]. According to this 'neural mechanism', episodes of progressive inflammation during the course of chronic pancreatitis may induce recurrent pain. The observation that a few patients had an episode of acute pain attributed to a documented relapse of pancreatitis in the follow-up period after splanchnicectomy could be an example of this theory. Third, recurrent pain may be related to previous opioid abuse. A return to alcohol and opioid use was identified at follow-up visits during the process of gradual tapering of pain medication, even some time after splanchnicectomy. It seems that in certain subgroups of patients with chronic pancreatitis addiction may interfere with the evaluation of the success of thoracoscopic splanchnicectomy. Fourth, splanchnicectomy has a placebo effect in some patients. This might explain the relatively large number of patients with pain recurrence within 1 year.

A long-term success rate of 50 per cent is lower than that reported by others[12], although a thorough comparison is not possible owing to differences in study design and endpoints used. The higher percentage of preoperative opioid use and the number of previous unsuccessful surgical procedures in this series may have influenced the outcome.

Leaving an enlarged head of the pancreas surgically untouched might be criticized because of the higher risk of pancreatic carcinoma in patients with chronic pancreatitis[20]. However, the overall incidence of carcinoma found unexpectedly after resection for chronic pancreatitis is very low[7,21]. For this reason, the authors believe that bilateral thoracoscopic splanchnicectomy may be performed in the presence of an enlarged pancreatic head.

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Original article

Serum amyloid A is a better early predictor of severity than C-reactive protein in acute pancreatitis

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Background: Serum amyloid A (SAA) is an early and sensitive marker of the extent of tissue trauma and inflammation. The aim of this study was to compare the early prognostic accuracy of SAA with that of serum C-reactive protein (CRP) in acute pancreatitis.

Methods: In a prospective multicentre trial, plasma SAA and CRP levels were measured in patients with severe and mild acute pancreatitis, and in a control group with acute abdominal pain. Plasma samples were collected on admission and at 6-h intervals for 48 h, every 12 h between 48 and 72 h, then daily for 5 days. Plasma SAA was measured by a new enzyme-linked immunosorbent assay and CRP was measured by immunoturbidometry.

Results: There were 137 patients with mild and 35 with severe acute pancreatitis, and 74 control patients. SAA levels were significantly higher in patients with severe acute pancreatitis than in those with mild acute pancreatitis, on admission, at 24 h or less after symptom onset, and subsequently. Whereas plasma CRP concentration was also significantly higher in patients with severe acute pancreatitis on admission, it failed to distinguish mild from severe acute pancreatitis until 30–36 h after symptom onset. SAA levels predicted severity (sensitivity 67 per cent, specificity 70 per cent, negative predictive value 89 per cent, mean(s.d.) area under curve 0·7(0·05)) significantly better than CRP (57 per cent, 60 per cent, 84 per cent, 0·59(0·06) respectively) on admission ($P = 0{\cdot}02$) and at 24 h following symptom onset (area under curve 0·65(0·09) *versus* 0·58(0·09) respectively; $P < 0{\cdot}02$).

Conclusion: Plasma SAA concentration is an early marker of severity in acute pancreatitis and is superior to CRP estimation on hospital admission and at 24 h or less after symptom onset. This study suggests that plasma SAA concentration is clinically useful, with the potential to replace CRP in the management of acute pancreatitis.

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Introduction

Acute pancreatitis is a disease characterized by inflammation and, sometimes, partial destruction of the pancreas followed by a systemic inflammatory reaction that may trigger systemic complications in the later course of the disease[1,2]. A severe attack affects 20–30 per cent of patients with acute pancreatitis, with a mortality rate of 30–50 per cent in this group[3]. Moreover, approximately 50 per cent of deaths occur within the first week of the attack, mostly from multiorgan dysfunction syndrome[2,4]. Improved outcome is based on early recognition of severe disease, permitting management in the high dependency or intensive care unit[5] and, in the case of gallstone-linked disease, an emergency endoscopic sphincterotomy[6,7]. Considerable difficulty exists in identifying severe cases within the first 2–3 days of symptom onset, a critical period during the establishment of multiorgan dysfunction[3,8].

The Acute Physiology And Chronic Health Evaluation (APACHE) II[9], Ranson[10] and Imrie[11] clinicobiochemical systems all have a similar accuracy 48 h after hospital

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The Editors have satisfied themselves that all authors have contributed significantly to this publication

admission but are not used routinely in most hospitals because they are cumbersome. A single marker would have considerable attraction for routine clinical practice. Many single markers have been assessed, including serum interleukin (IL) 8[12], IL-6[13], procalcitonin[12,14], tumour necrosis factor (TNF)[15], phospholipase A_2[16], C-reactive protein (CRP)[16], trypsin 2 and α_1-antitrypsin complex[17], anionic trypsinogen[18], and the activation peptides of carboxypeptidase B[18] and cationic trypsinogen (TAP)[19]. Of these, only CRP is in routine clinical use, but it is predictive only 48–72 h after the onset of symptoms, with an accuracy of around 70 per cent[12,13,15,16,19]. Although TAP has been shown to have a high negative predictive value (86–94 per cent) for the first 3 days after the onset of symptoms[19], widespread routine application awaits the introduction of an automated assay. Thus there is considerable scope for the assessment of novel prognostic markers for acute pancreatitis.

CRP and serum amyloid A (SAA) are the two major acute-phase proteins in humans; their level increases up to 1000-fold, compared with 50-fold for a large number of other acute-phase proteins[20]. Although much is known about SAA, its biological role is still not clearly defined. SAA consists of a family of apolipoproteins that bind rapidly to acute-phase high-density lipoprotein and can influence cholesterol metabolism during inflammatory states[20]. There are two genetic loci producing six isoforms by transcriptional and post-translational mechanisms. The liver produces large amounts of SAA during microbial infection and in various other inflammatory states[21]. SAA induces chemotaxis of polymorphonuclear cells (PMNs), monocytes and T lymphocytes, activates PMNs, and causes the release of TNF-α, IL-1β and IL-8 from PMNs[21,22]. In both clinical and experimental studies, SAA has also been reported to be a very early marker of inflammation and tissue injury in a variety of conditions; in general, changes in SAA mirror those of CRP but in some circumstances may be greater[20,23–27].

Recently two investigations have compared the prognostic value of SAA with CRP and procalcitonin in acute pancreatitis, but with limited conclusions because of the relatively small size of the studies[28,29]. Here, the first large study of SAA levels in patients with severe or mild acute pancreatitis, and in a control group with various gastrointestinal diseases, is reported.

Patients and methods

Study design

This study was part of a prospective European multicentre study that validated the prognostic value of urinary TAP in acute pancreatitis in comparison with CRP and established clinicobiochemical scoring systems[19]. Consecutive patients were recruited from the University Hospital of Ulm (Germany), the Royal Liverpool University Hospital (UK), the Helsinki University Central Hospital (Finland) and the Mater Misericordiae Hospital in Dublin (Ireland). Patients were admitted to the study after giving informed consent. Before the study each centre obtained local research ethics committee approval.

Patients with acute abdominal pain of uncertain diagnosis or suspected acute pancreatitis were recruited. Exclusion criteria were previous abdominal surgery for pancreatitis, pancreatic resection, pre-existing chronic pancreatitis, age less than 18 years and tertiary referral. The time of onset of abdominal pain was determined prospectively. Acute pancreatitis was defined as acute abdominal pain with a typical clinical picture and a serum amylase level at least three times the upper limit of normal and/or typical findings on computed tomography or ultrasonography. Patients who were admitted with acute abdominal pain but did not have a final diagnosis of acute pancreatitis were recruited in parallel as controls. The same exclusion criteria applied as for patients with acute pancreatitis. The time of onset of symptoms in patients with acute pancreatitis and in controls was determined immediately on entry into the study (i.e. at the time of review in the emergency admissions area).

Severity was defined according to the Atlanta Classification[30]. The APACHE II[9] scores were determined on admission and on days 1, 2 and 3 after admission; the Ranson[10] and Glasgow[11] scores were determined 48 h after admission.

An investigators meeting was held to review each patient and to ascertain eligibility after closing the study. The clinical severity in patients with acute pancreatitis[30] was checked without knowledge of any experimental data.

Sample collection

For experimental analysis, blood and urine samples were obtained on admission and at 6 h intervals for 48 h, then every 12 h up to 72 h and finally daily for another 5 days after admission. Plasma samples were collected into ethylenediamine tetra-acetic acid, centrifuged within 60 min and stored at – 70°C; urine samples were also stored at – 70°C.

Plasma C-reactive protein measurements

Plasma CRP concentration was measured using an immunoturbidimetric assay (Boehringer, Mannheim, Germany) on an automated analyser (Hitachi 747; Hitachi, San Jose, California, USA). The reference range is less than 5 mg/l, and intra-assay and interassay variations are less than 5 per cent. All CRP measurements were performed at the Royal Liverpool University Hospital.

Plasma serum amyloid A measurements

Plasma SAA was determined using a newly developed enzyme-linked immunosorbent assay (Biotrin, Dublin, Ireland). The reference range is less than 1 mg/l; the intra-assay variation is 3·9 per cent and the interassay variation 7·5 per cent. Samples with SAA levels higher than 1200 mg/l (upper limit) were diluted. All samples were measured at Biotrin.

Statistical analysis

Categorical data were analysed with the χ^2 test and Fisher's exact test. Continuous non-parametric data were calculated as median and interquartile range or 95 per cent confidence interval (c.i.) for the median, and analysed with the Kruskal–Wallis and Mann–Whitney *U* tests. Receiver–operator characteristic (ROC) curves were constructed for the prognostic value of SAA and analysed by comparing the area under the curve (AUC)[31]. Because there is no prognostic standard level for SAA, optimum cut-off levels using ROC curves were determined on admission, at 24 h or less, at 48 h or less, and at 120 h after hospital admission. In order not to bias the results in favour of SAA, optimum levels were also calculated in a similar manner in this series for CRP. $P < 0.05$ was considered statistically significant.

Results

Patients

A total of 303 patients were enrolled into the study; 57 of these were excluded because they did not meet all the eligibility criteria. Some 172 of the remaining 246 eligible patients suffered from acute pancreatitis and 74 were controls.

The overall median age of patients with acute pancreatitis was 52 (95 per cent c.i. 29 to 84) years; 87 were men. Overall, 137 of the patients had mild disease and the remaining 35 (20 per cent) had severe disease (Atlanta classification[30]). The aetiology was gallstones in 74 patients (66 mild, eight severe), of whom 50 were women and 24 were men with a median age of 65 (95 per cent c.i. 37 to 86) years. Alcohol was the cause in 62 patients (39 mild, 23 severe), of whom 12 were women and 50 were men with a median age of 45 (95 per cent c.i. 32 to 64) years. The other 36 patients (32 mild, four severe) had miscellaneous causes; 23 were women and 13 were men with a median age of 53 (95 per cent c.i. 24 to 84) years. The overall median (95 per cent c.i.) hospital stay was 8 (3 to 55) days: 22 (2 to 102) days in severe cases and 7 (3 to 19) days in mild cases ($P < 0.001$), with no significant differences according to aetiology. In the severe pancreatitis group, 16 patients had more than 30 per cent pancreatic necrosis as determined by contrast-enhanced computed tomography, 11 had adult respiratory distress syndrome and eight had multiorgan failure. Eight of the 35 patients with severe acute pancreatitis died.

The distribution of cases by centre is shown in *Table 1*. The centres in Ulm and Liverpool had relatively more cases resulting from gallstones (ten (83 per cent) of 12 and 48 (62 per cent) of 77 respectively) compared with Dublin and Helsinki (one (6 per cent) of 16 and 15 (22 per cent) of 67 respectively); conversely the latter centres had proportionately more cases due to alcohol (ten (63 per cent) of 16 and 39 (58 per cent) of 67 respectively) compared with the former centres (one (8 per cent) of 12 and 12 (16 per cent) of 77 respectively; $\chi^2 = 47.5$, 6 d.f., $P < 0.001$). There were relatively more severe cases in Ulm and Helsinki (four (33 per cent) of 12 and 20 (30 per cent) of 67 respectively) compared with Dublin and Liverpool (one (6 per cent) of 16 and ten (13 per cent) of 77 respectively; $\chi^2 = 9.52$, 3 d.f., $P = 0.023$). The median (95 per cent c.i.) delay from symptom onset to hospital admission was 13 (1 to 73) h. Recruitment by the Liverpool centre of patients with acute pancreatitis (both mild and severe cases) occurred significantly more quickly following the onset of symptoms than in the other centres ($P < 0.001$; *Table 1*).

The median age of the controls was 47 (95 per cent c.i. 24 to 79) years; 39 were women. The median admission delay for control patients was 21 (95 per cent c.i. 3 to 198) h with no significant differences between the centres in terms of presentation (*Table 1*). Only two patients had a serum amylase level more than three times the upper limit of normal. The final diagnoses for control patients were as follows: non-specific abdominal pain, 17; gastritis, ten; biliary colic, ten; subacute intestinal obstruction, seven; acute cholecystitis, six; obstructive jaundice, four; acute appendicitis, four; peptic ulcer, two; diverticulitis, two; and one case each of Gram-negative septicaemia, torted ovarian cyst, colonic liponecrosis, internal hernia, urinary retention, ureteric colic (stone), caecal volvulus, pneumonia, Crohn's disease, constipation, mesenteric infarction and abdominal aortic aneurysm.

Acute Physiology And Chronic Health Evaluation II, Ranson and Glasgow scores

The median (95 per cent c.i.) APACHE II score at 48 h following hospitalization for mild acute pancreatitis was 7 (6 to 8); for severe acute pancreatitis it was 11 (7 to 13)

Table 1 Aetiology, severity and delay in hospitalization in patients with acute pancreatitis and in control subjects from the onset of symptoms by recruitment centre

	Aetiology of acute pancreatitis				
	Gallstones	Alcohol	Miscellaneous	Total no. of patients	Median delay (h)
Severe AP					
Ulm	4	0	0	4	28 (4, 70)
Dublin	0	1	0	1	23
Liverpool	2	5	3	10	5 (1, 13)
Helsinki	2	17	1	20	26 (4, 64)
All	8	23	4	35	15 (3, 62)
Mild AP					
Ulm	6	1	1	8	25 (5, 41)
Dublin	1	9	5	15	18 (1, 277)
Liverpool	46	7	14	67	7 (1, 27)
Helsinki	13	22	12	47	24 (2, 76)
All	66	39	32	137	12 (1, 73)
Controls					
Ulm	—	—	—	0	—
Dublin	—	—	—	6	16 (4, 266)
Liverpool	—	—	—	34	14 (4, 58)
Helsinki	—	—	—	34	26 (2, 282)
All	—	—	—	74	21 (3, 198)

Values in parentheses are 95 per cent confidence intervals. AP, acute pancreatitis

(P = 0·01, severe *versus* mild) and for controls it was 5 (4 to 7) (P = 0·3, control *versus* mild; P = 0·001, control *versus* severe). Similarly the median (95 per cent c.i.) Glasgow scores for mild and severe acute pancreatitis were 1 (1 to 2) and 4 (3 to 4) respectively (P < 0·001) and the Ranson scores were 2 (1·5 to 2) *versus* 4 (3 to 5) respectively (P < 0·001).

Plasma C-reactive protein and serum amyloid A levels

The time course for values of plasma CRP and SAA adjusted according to the onset of symptoms are shown in *Figs 1* and *2*. Seventy-two patients had analysis performed within less than 24 h of symptom onset (12 patients with severe and 40 with mild acute pancreatitis, and 20 controls). One hundred and sixty-one patients had analysis performed 24–48 h after symptom onset (26 patients with severe and 105 with mild acute pancreatitis, and 30 controls). The serum CRP values for both severe and mild acute pancreatitis were not significantly different from those of controls until 48 h following symptom onset (*Fig. 1*). The SAA values, however, differed significantly in severe pancreatitis from those in both mild pancreatitis and controls (P < 0·001) from the onset of symptoms (*Fig. 2*). In mild pancreatitis the SAA values also differed significantly from controls overall, but only from 48 h up to 120 h after symptom onset ($P \leqslant$ 0·01) (*Fig. 2*). There were no significant differences in the TAP or SAA results according to aetiology.

The maximum values for plasma CRP and SAA on hospital admission and up to 24, 48 and 120 h after symptom onset are shown in *Table 2*. Both markers significantly differentiated severe acute pancreatitis from mild disease on hospital admission. However, only plasma SAA concentration was able to predict the outcome significantly within the first 24 h after symptom onset. The levels of accuracy of the prediction of severity for plasma CRP and SAA are summarized in *Table 3*. Based on the differences for the AUCs derived from the ROCs, plasma SAA levels were significantly better than plasma CRP at predicting severity on hospital admission and also at 24 h after the onset of symptoms ($P \leqslant$ 0·02).

Discussion

This study has shown that plasma levels of SAA can be used to predict the severity of acute pancreatitis significantly earlier and better than plasma CRP levels. The finding of an earlier acute rise in circulating levels of SAA compared with CRP is in accordance with data emerging from studies in other inflammatory disease states[24,27].

SAA has been found to be a marker of the intensity of tissue damage in trauma patients and of the degree of inflammation in a variety of acute and chronic inflammatory states[23–27]. The potential sensitivity of SAA has been demonstrated by its ability to predict myocardial infarction in the general population[32,33]. In a study comparing 3000

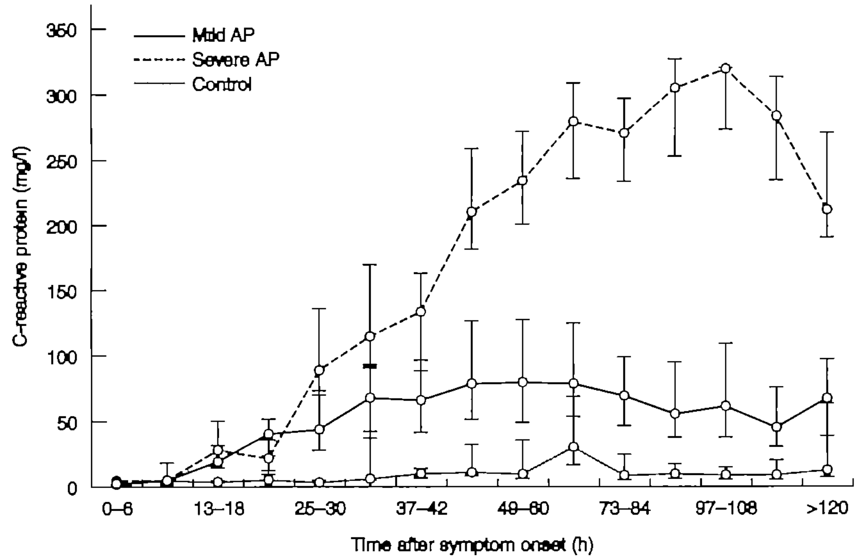

Fig. 1 C-reactive protein levels after the onset of symptoms in patients with mild and severe acute pancreatitis (AP), and in control patients. Values are median (interquartile range). $P < 0.001$ (severe *versus* mild AP, mild *versus* control) only after 48 h following symptom onset (Kruskal–Wallis and Mann–Whitney *U* tests)

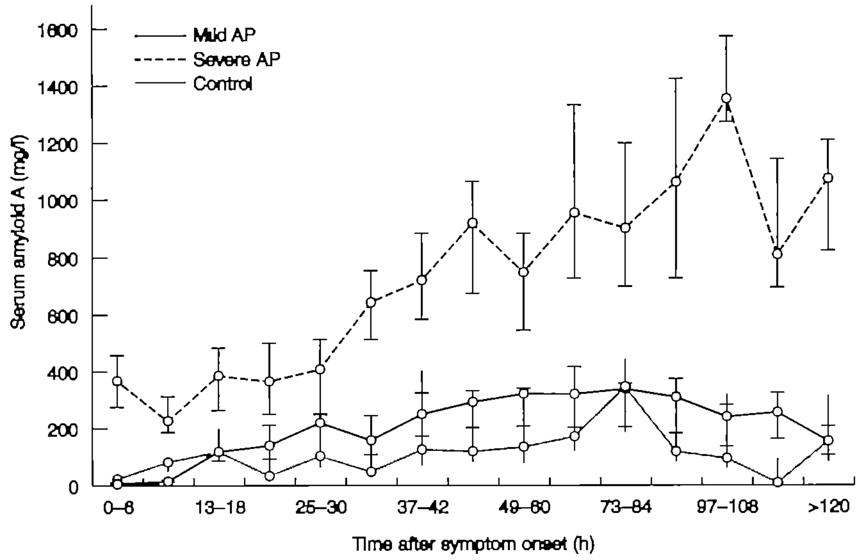

Fig. 2 Serum amyloid A concentration after the onset of symptoms in patients with mild and severe acute pancreatitis (AP), and in control patients. Values are median (interquartile range). $P < 0.001$ (severe *versus* mild AP and control from the outset); $P \leq 0.01$ (mild *versus* control overall from 48 to 120 h) (Kruskal–Wallis and Mann–Whitney *U* tests)

parallel measurements of SAA and CRP in various disease states, SAA concentration was found to have a close relationship to CRP level but was more sensitive in reflecting inflammatory activity[24]. In rheumatic disorders, SAA concentration may be raised even when CRP is not detectable[25]. Similarly, SAA is an early and sensitive marker for allograft organ rejection, being increased when CRP levels are frequently in the normal range or only slightly raised[34,35]. SAA is a useful parameter for assessing the acute inflammatory reaction and early prediction of complica-

Table 2 Maximum plasma C-reactive protein and serum amyloid A levels in patients with mild and severe acute pancreatitis, and in controls on admission and at less than 24, 48 and 120 h after symptom onset

	Mild acute pancreatitis	Severe acute pancreatitis	Control
On admission			
Plasma CRP (mg/l)	30 (24, 47)*†	65 (9·7, 196)†	8·5 (7·5, 15)
Plasma SAA (mg/l)	116·6 (77, 214)*	675 (295, 1129)†	83·9 (46, 161)
≤ 24 h after symptom onset			
Plasma CRP (mg/l)	25 (8, 54)	23 (2·5, 61)	4·25 (2·5, 11)
Plasma SAA (mg/l)	79 (30, 160)‡	304 (98, 757)§	68 (9, 135)
≤ 48 h after symptom onset			
Plasma CRP (mg/l)	72 (47, 107)*†	200 (132, 270)†	7 (2·5, 13)
Plasma SAA (mg/l)	412 (271, 557)¶**	937 (590, 1312)†	108 (47, 153)
≤ 120 h after symptom onset			
Plasma CRP (mg/l)	124 (101, 157)*†	345 (303, 385)†	13 (6, 24)
Plasma SAA (mg/l)	659 (495, 895)*†	1711 (1309, 2168)†	129 (73, 430)

Values are median (95 per cent confidence intervals). CRP, C-reactive protein; SAA, serum amyloid A. $^*P < 0{\cdot}001$ *versus* severe, $^\dagger P \leq 0{\cdot}001$ *versus* control, $^\ddagger P = 0{\cdot}009$ *versus* severe, $^\S P = 0{\cdot}005$ *versus* control, $^\P P = 0{\cdot}004$ *versus* severe, $^{**}P = 0{\cdot}002$ *versus* control (Mann–Whitney *U* test)

Table 3 Prognostic accuracy of plasma C-reactive protein and serum amyloid A levels on hospital admission and at less than 24, 48 and 120 h after symptom onset

Optimum plasma cut-off level	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Area under curve*
On admission						
CRP >48 mg/l	57	60	27	84	59	0·59(0·06)†
SAA >418 mg/l	67	70	36	89	69	0·70(0·05)
≤ 24 h after symptom onset						
CRP >28 mg/l	75	50	31	87	47	0·58(0·09)†
SAA >185 mg/l	58	62	32	83	56	0·65(0·09)
≤ 48 h after symptom onset						
CRP >120 mg/l	73	66	34	91	68	0·73(0·06)
SAA						
> 360 mg/l	96	49	30	98	61	0·75(0·06)
> 475 mg/l	80	58	32	92	64	—
≤ 120 h after symptom onset						
CRP >300 mg/l	71	89	64	92	85	0·85(0·04)
SAA >1200 mg/l	79	80	49	94	80	0·82(0·05)

*Values are mean(s.d.). CRP, C-reactive protein; SAA, serum amyloid A; PPV, positive predictive value; NPV, negative predictive value. $^\dagger P \leq 0{\cdot}02$ *versus* SAA[31]

tions after cardiac surgery[36]. It is against such a background that there has been recent interest in assessing the potential value of SAA in acute pancreatitis[28,29].

The variation in aetiology between centres may confound the results of investigating prognostic factors in acute pancreatitis. This bias was minimized in the present study by using four different centres with known different patterns of disease. The results showed that prognostication using SAA and CRP was unrelated to aetiology. The dynamic change of prognostic markers over the natural course of acute pancreatitis is another major confounding factor. Spurious differences between series may arise because of the variation in time to presentation, highlighted by the findings in this study. Therefore the results were standardized against the time of onset of symptoms (determined at the time of hospital admission), thereby minimizing differences between centres. Control of the time variable by use of this method is important, as this will enable direct interpretation with future series.

Comparison of the present study with the two previous studies of SAA in acute pancreatitis[28,29] also needs to take into account the lack of an accepted prognostic cut-off value for SAA. This is because the use of SAA to predict severity in acute pancreatitis is a relatively new concept. This poses a potential pitfall for the comparison with other prognostic variables, in this case serum CRP concentration. A commonly used cut-off level for CRP is 150 mg/l[13,19], with alternative values varying from 100 to 200 mg/l also proposed. In order not to bias results against CRP, the two other recent studies[28,29] as well as the present study compared cut-off levels for both SAA and CRP that were optimized in each of the respective studies.

Rau *et al.*[28], in a study of 66 patients with acute pancreatitis (39 with necrotizing pancreatitis), found that serum SAA concentrations increased more quickly than the levels of CRP. The SAA levels, like CRP, were significantly higher in patients who developed pancreatic necrosis, infected pancreatic necrosis and multiple organ dysfunction syndrome, and in those who died. Serum SAA level was a better predictor of necrotizing pancreatitis, whereas serum CRP concentration was better at predicting infected pancreatic necrosis, multiple organ dysfunction syndrome and death. The AUCs for these four outcome measures for serum SAA in the first week were in the range of 0·62–0·71 (cut-off points 400–460 mg/l), compared with 0·82 (cut-off point 1200 mg/l) for severity prediction in the first 5 days of this study. The corresponding AUC range for serum CRP reported by Rau *et al.*[28] was 0·71–0·78 (cut-off points 180–230 mg/l), compared with 0·85 (cut-off point 300 mg/l) in the present study. Pezzilli *et al.*[29] studied 31 patients with acute pancreatitis (12 with a severe attack) and reported the sensitivity, specificity and overall accuracy for SAA (cut-off 240–250 mg/l) as 77, 69 and 72 per cent respectively. The respective values for procalcitonin (cut-off 0·252–0·255 ng/ml) were 22, 83 and 58 per cent, and those for CRP (cut-off 128–129 mg/l) were 61, 89 and 78 per cent. Taken together these studies[28,29], together with the present results, suggest that SAA levels are at least as good as CRP concentration in predicting outcome, but that circulating SAA levels rise faster than CRP. Indeed this study, which was designed to assess early prognostic value, showed that SAA concentration was significantly better than CRP level at predicting outcome at the time of hospital admission and also within 24 h of symptom onset. These findings are consistent with the fact that levels of SAA appear to rise more quickly than those of CRP in endoscopic retrograde cholangiopancreatography (ERCP)-induced acute pancreatitis[37,38].

In acute pancreatitis, release of the major acute-phase proteins (notably CRP and SAA) from the liver is induced by cytokines (chiefly IL-6), and the acute-phase proteins in turn induce the release of other inflammatory cytokines[2,39] such as TNF-α and IL-8 in the case of SAA[20,22]. Oezcueruemez-Porsch *et al.*[37] found that in ERCP-induced acute pancreatitis serum levels of IL-1 receptor antagonist (IL-1ra) peaked at 2 h, levels of IL-6 peaked at 6 h, and levels of SAA peaked at 24 h after the onset of symptoms. In a similar study by Messmann *et al.*[38] the circulating level of IL-1ra peaked at 12 h, the level of IL-6 peaked at 24 h and that of CRP peaked at 72 h.

Given the degree of rise of both of these acute-phase proteins, it is highly likely that SAA and CRP are major players in the pathogenesis of acute pancreatitis. From an early prognostic viewpoint, however, SAA appears to be superior to CRP. A necessary future objective would be to establish a widely acceptable and, ideally, single prognostic cut-off level for SAA. Given the critical role of trypsinogen activation in the early pathogenesis of acute pancreatitis[39–43], it is likely that TAP is still the most potentially powerful single early marker of severity in acute pancreatitis[19]. Nevertheless, it seems that there may be distinct roles for the use of both TAP and an acute-phase inflammatory marker in the overall management of patients with acute pancreatitis. The results of this study suggest that measurement of circulating SAA levels may prove to be superior to measurement of CRP concentration. Further large studies of plasma levels of SAA in acute pancreatitis are warranted.

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Original article

Role of mast cells in the development of pancreatitis-induced multiple organ dysfunction

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Background: Activated mast cells can produce and release a number of inflammatory mediators involved in the pathophysiology of acute conditions. The aim of the present study was to evaluate the role of activated tissue mast cells in the pathogenesis of multiple organ dysfunction syndrome following acute pancreatitis (AP).

Methods: AP was induced by the intraductal infusion of 5 per cent sodium taurodeoxycholate in the rat. Some 30 min before induction of AP, a mast cell stabilizer (sodium cromoglycate (SCG)) or antihistamines (pyrilamine, cyproheptadine, meclizine and amitriptyline) were administered intraperitoneally. Plasma exudation of radiolabelled albumin, histamine, myeloperoxidase (MPO), monocyte chemoattractant protein (MCP) 1 and adhesion molecules (platelet endothelial cell adhesion molecule (PECAM) 1 and L-selectin) were measured.

Results: The mast cell stabilizer significantly reduced plasma exudation in the pancreas, colon and lungs ($P < 0{\cdot}05$), decreased the release of histamine at 1 h ($P < 0{\cdot}05$), and reduced MPO activity and MCP-1 levels in the colon and lungs ($P < 0{\cdot}05$) but not in the pancreas. Expression of PECAM-1 and L-selectin on total circulating leucocytes in rats with AP and SCG pretreatment did not differ from that in sham controls, while levels in animals that had AP and saline pretreatment were half of those seen following sham operation.

Conclusion: Activation of mast cells after induction of AP is involved in the development of endothelial barrier dysfunction in both the pancreas and extrapancreatic organs/tissues, particularly in the lungs and colon. This may, at least partly, contribute to the sequential development of multiple organ dysfunction and organ/tissue-specific endothelial barrier dysfunction.

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Introduction

Acute pancreatitis (AP) is a common disorder with a yearly incidence of 50–500 attacks per million inhabitants[1]. Acute lung injury and pancreatic sepsis, associated with increased permeability and enteric bacterial translocation into extra-intestinal sites and the systemic circulation (gut origin sepsis)[2,3], are major contributory factors to death and morbidity in severe AP. Underlying mechanisms for the local initiating events in the pancreas, the systemic dissemination of the inflammatory response and remote organ dysfunction in AP are still not fully elucidated, but involve a variety of cells and mediators including cytokines. Mast cells are found closely apposed to the vasculature in essentially all tissues. Once activated, mast cells release preformed cytokines, histamine and serotonin as well as newly synthesized platelet activating factor, leukotrienes and possibly other mediators[4,5]. Thus, mast cells potentially play a central role in the initiation of the inflammatory response[4] characterized by microvascular changes, including increased vascular permeability and leucocyte accumulation[6]. The objective of the present study was to determine the effects of mast cells *in vivo* on: (1) local (pancreatic) injury; (2) multiple organ/tissue injury, e.g. in the lungs and the gut; (3) leucocyte recruitment (myeloperoxidase (MPO)); (4) chemokine release (monocyte chemoattractant protein (MCP) 1); and (5) adhesion molecule expression on circulating leucocytes in severe AP. Sodium cromoglycate (SCG; cromolyn)[6–10] used in this study is one of the most effective inhibitors of histamine release (associated with degranulation) from activated mast cells[11], delaying and almost entirely reducing the degranulation of mast cells[9], and inhibiting mediator release from mast cells[7,8]. The role of histamine was evaluated by using a number of different antihistamines with different specificity and receptor affinity, e.g. amitriptyline[12,13], cyproheptadine[12–15], pyrilamine[16] and meclizine[15].

Materials and methods

Animals

Adult male Sprague–Dawley rats, weighing about 250 g, were fed rat chow (R3; Astra-Ewos, Södertälje, Sweden) and water *ad libitum*. The protocol was approved by the Animal Ethics Committee at Lund University.

Induction of acute pancreatitis

The rats were operated on under aseptic conditions using an intramuscular mixture of ketamine 70 mg/kg and rompun 25 mg/kg (Sigma Aldrich, Stockholm, Sweden) anaesthesia. Acute pancreatitis was induced by the intraductal infusion of 0·2 ml 5 per cent sodium taurodeoxycholate by the use of an infusion pump at a speed of 0·04 ml/min following clamping of the proximal end of the common bile duct, and cannulating the biliary–pancreatic duct. Sham operation (control) included laparotomy and isolation of the common bile duct without bile salt injection.

The animals were allocated randomly into the following groups: 1-h model (sham operation (control) or AP pretreated with saline, SCG or one of the antihistamines) or 6-h model (sham operation (control) or AP pretreated with saline or SCG). All drugs were from Sigma Aldrich and were administered intraperitoneally 30 min before sham operation or induction of AP. There were six surviving animals in each group. Evaluation was performed 1 and 6 h after induction of AP.

Measurement of capillary endothelial permeability

The endothelial permeability in the pancreas and other organs studied was assessed by the leakage of ^{125}I-radiolabelled human serum albumin (HSA) (Institute for energiteknik, Kjeller, Norway) from blood to the pancreatic tissue. Some 0·5 ml ^{125}I-labelled HSA ($1{\cdot}8 \times 10^6$ c.p.m.) was injected into the femoral vein. After 1 h equilibration, 0·3 ml blood was drawn from the femoral artery followed by injection of 0·5 ml ^{131}I-radiolabelled HSA ($1{\cdot}8 \times 10^6$ c.p.m.). The animals were killed by an overdose of pentobarbitol 5 min after the ^{131}I-labelled HSA injection. Blood (0·3 ml from the femoral artery and 2·5 ml from the abdominal aorta) was drawn before killing the animal. Tissue samples were harvested, cleared of external blood and weighed. The radioactivity of ^{125}I (half-life 1430 h) and ^{131}I (half-life 192 h) in blood and tissue samples was measured in a γ counter (1272 Clinigamma; LKB, Wallac, Finland). Capillary endothelial permeability was assessed by leakage of ^{125}I-radiolabelled HSA from blood into the tissues and expressed as isotopic flux, defined as the proportion of ^{125}I radioactivity per gram tissue sample compared with radioactivity per gram blood as described previously[3].

Measurement of leucocyte recruitment (myeloperoxidase)

Tissue samples (100–200 mg) were weighed, put in ice-cold potassium phosphate buffer 20 mmol/l (pH 7·4) and homogenized for 30 s. The suspension was centrifuged at 20 000 r.p.m. for 15 min at 4°C, after which the supernatant was discarded. The precipitates were rehomogenized with phosphate-buffered saline (PBS) 50 mmol/l containing 0·5 per cent hexadecyltrimethylammonium bromide and ethylenediamine tetra-acetic acid 10 mmol/l, followed by sonicating, freezing, thawing and homogenizing twice. The reaction was terminated with sodium acetate 0·2 mol/l (pH 3·0), after incubation for 3 min at 37°C with a reaction solution containing 0·5 per cent hexadecyltrimethylammonium bromide, 3,3,5,5-tetramethylbenzidine 1·6 mmol/l and hydrogen peroxide 0·3 mmol/l in PBS 80 mmol/l (pH 5·4)[17]. MPO activity was measured as the change in absorbance at 655 nm per minute.

Histamine assay

Histamine was measured using an enzyme immunoassay kit (Immunotech, Marseille, France) according to the manufacturer's instructions.

Assay of monocyte chemoattractant protein and tumour necrosis factor α

Supernatant levels of MCP-1 and tumour necrosis factor (TNF) α were determined by enzyme-linked immunosorbent assay. Antibodies specific for rat MCP-1 and TNF-α (Pharmingen, San Diego, California, USA) were coated on to the wells of microtitre strips (NUNC, Copenhagen, Denmark) and the samples, including standards of known rat MCP-1 and TNF-α, were pipetted into the wells, incubated and washed. Intensity of the colour was determined at 405 nm.

Flow cytometry

The cells were washed twice and stained with fluorescein isothiocyanate- or phycoerythrin-conjugated monoclonal antibodies directed against cell surface molecules. Mouse monoclonal antibodies directed against rat CD11b (WT.5), CD11b/c (OX-42), platelet endothelial cell adhesion molecule (PECAM) 1 (TLD-3A12), CD54 (1A29) and L-selectin (HRL1) were purchased from Pharmingen. Cell staining was performed in PBS with 1 per cent bovine serum albumin (PBS–BSA) on ice. Cells were washed twice in PBS–BSA after each incubation step and kept on ice until flowcytometry analysis.

Statistical analysis

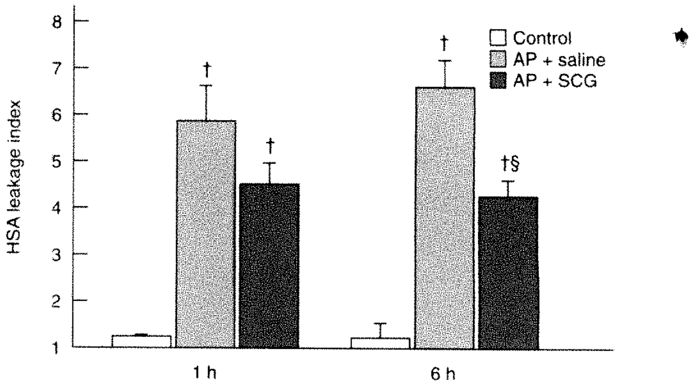
Values are expressed as mean(s.e.m.). Unpaired, two-tailed Student's *t* test was used for statistical analysis. $P < 0·05$ was considered significant.

Results

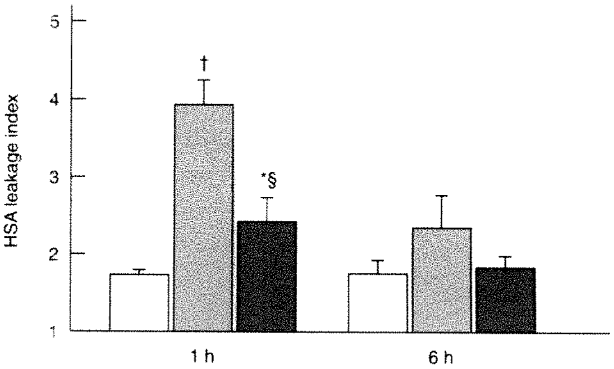
The leakage index of radiolabelled HSA in animals with pancreatitis pretreated with saline was significantly higher than that in sham-operated animals (control) in both the pancreas and colon 1 h after induction ($P < 0·01$), and in the pancreas and lungs after 6 h ($P < 0·05$) (*Fig. 1*). The mast cell stabilizer (SCG) significantly reduced plasma exudation in the pancreas at 6 h after induction of AP, in the colon after 1 h and in the lungs after 6 h ($P < 0·05$). Pancreatic and colonic water content measured 1 and 6 h after induction of pancreatitis increased significantly in animals with pancreatitis pretreated with saline compared with sham-operated animals ($P < 0·05$) (*Fig. 2*). Pretreatment with the mast cell stabilizer SCG significantly decreased water content at 1 h in the pancreas and at both 1 and 6 h in the colon after induction of AP ($P < 0·05$), while the decrease in pulmonary water content did not reach statistical significance.

Mast cell activation was assessed by measuring the plasma histamine level, which was significantly increased in animals with pancreatitis pretreated with saline 1 h after induction of AP ($P < 0·05$). The histamine level was significantly lower in animals pretreated with the mast cell stabilizer ($P < 0·05$). However, none of the antihistamines used had any effect on the pancreatic HSA leakage index (data not shown).

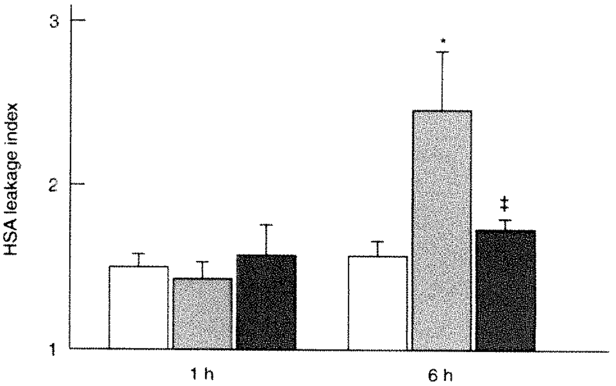
Tissue leucocyte recruitment, assessed by MPO activity, significantly increased in the colon and lungs at 1 and 6 h ($P < 0·01$), and in the pancreas at 6 h after induction of AP in animals pretreated with saline ($P < 0·01$) (*Fig. 3*). Pretreatment with the mast cell stabilizer (SCG) significantly decreased tissue MPO activity in the colon at 1 and 6 h ($P < 0·05$), and in the lungs 1 h after induction of AP ($P < 0·01$), but at neither time point in the pancreas.



a Pancreas

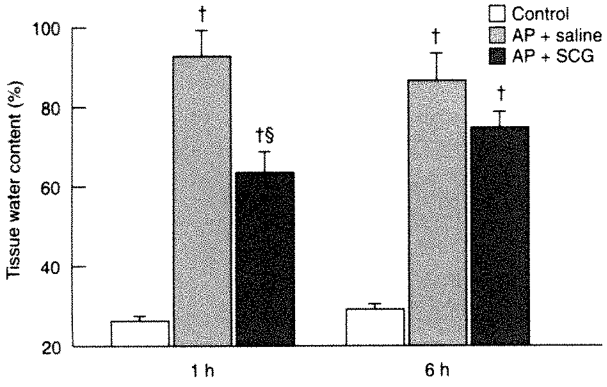


b Colon

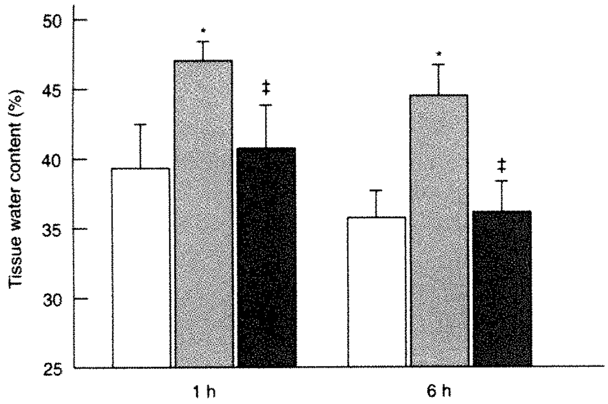


c Lung

Fig. 1 Human serum albumin (HSA) leakage index in **a** pancreas, **b** colon and **c** lungs 1 and 6 h after sham operation (control) or induction of acute pancreatitis (AP) following pretreatment with saline or sodium cromoglycate (SCG). Values are expressed as mean(s.e.m.). $^*P < 0·05$, $^†P < 0·01$ *versus* control; $^‡P < 0·05$, $^§P < 0·01$ *versus* pretreatment with saline ($n = 6$ surviving rats) (Student's *t* test)



a Pancreas



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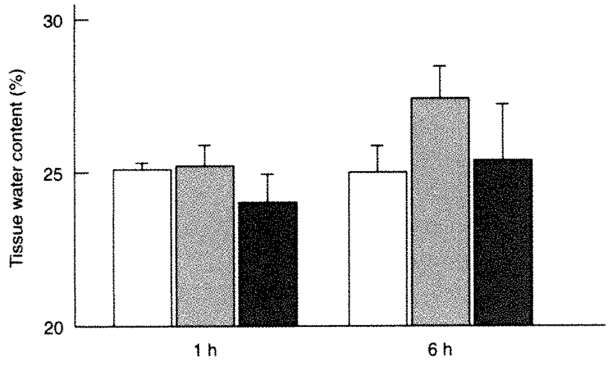
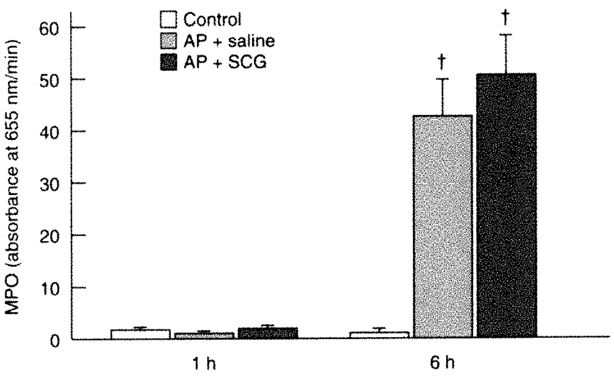
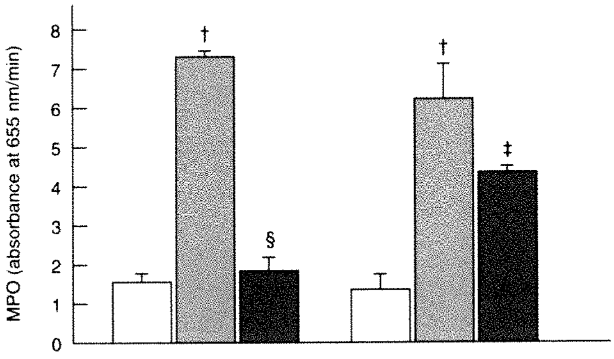


c Lung

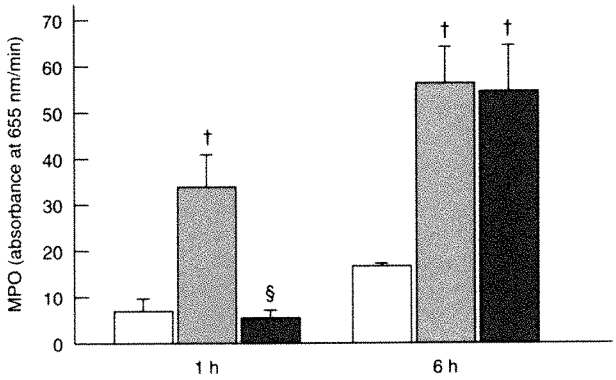
Fig. 2 Water content in **a** pancreas, **b** colon and **c** lungs 1 and 6 h after sham operation (control) or induction of acute pancreatitis (AP) following pretreatment with saline or sodium cromoglycate (SCG). Values are expressed as mean(s.e.m.). $*P < 0{\cdot}05$, $\dagger P < 0{\cdot}01$ *versus* control; $\ddagger P < 0{\cdot}05$, $\S P < 0{\cdot}01$ *versus* pretreatment with saline ($n = 6$ surviving rats) (Student's t test)



a Pancreas



b Colon

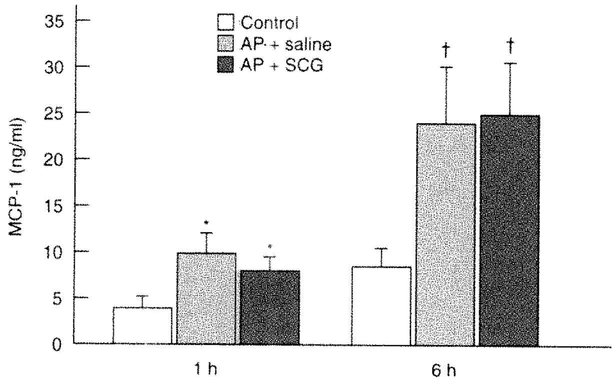


c Lung

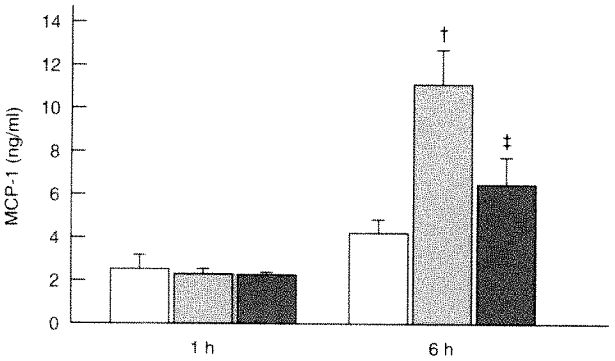
Fig. 3 Tissue myeloperoxidase (MPO) content in **a** pancreas, **b** colon and **c** lungs 1 and 6 h after sham operation (control) or induction of acute pancreatitis (AP) following pretreatment with saline or sodium cromoglycate (SCG). Values are expressed as mean(s.e.m.). $\dagger P < 0{\cdot}01$ *versus* control; $\ddagger P < 0{\cdot}05$, $\S P < 0{\cdot}01$ *versus* pretreatment with saline ($n = 6$ surviving rats) (Student's t test)

Tissue chemokine (MCP-1) levels in the pancreas and lungs significantly increased 1 and 6 h after induction of AP in animals pretreated with saline, and in the colon at 6 h ($P < 0{\cdot}05$) (*Fig. 4*). Pretreatment with SCG significantly decreased tissue MCP-1 levels in the lungs at 1 and 6 h, and in the colon 6 h after induction of AP ($P < 0{\cdot}05$).

TNF-α levels in the pancreas and lungs significantly increased ($P < 0{\cdot}05$) 1 and 6 h after induction of AP in



a Pancreas



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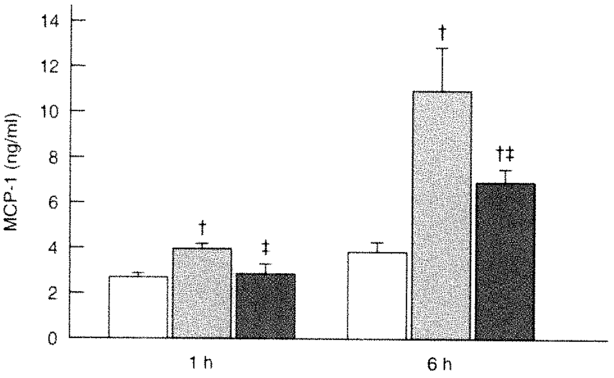

c Lung

Fig. 4 Tissue monocyte chemoattractant protein (MCP) 1 content in **a** pancreas, **b** colon and **c** lungs 1 and 6 h after sham operation (control) or induction of acute pancreatitis (AP) following pretreatment with saline or sodium cromoglycate (SCG). Values are expressed as mean(s.e.m.). $^*P < 0.05$, $\dagger P < 0.01$ *versus* control; $\ddagger P < 0.05$ *versus* pretreatment with saline ($n = 6$ surviving rats) (Student's t test)

animals pretreated with saline. These levels were not reduced after pretreatment with SCG (data not shown).

Flow cytometry results showed that the expression of PECAM-1 and L-selectin on circulating leucocytes 6 h after induction of AP in animals pretreated with saline was half of that seen in sham-operated animals (control), while their expression did not differ from controls following SCG pretreatment (data not shown). Most of these adhesion molecules were expressed on neutrophils and monocytes.

Discussion

Pancreatic endothelial barrier dysfunction represents an initial and characteristic event in the development of pancreatic interstitial oedema and injury. Changes in endothelial barrier function, including an increase in endothelial permeability, release of inflammatory mediators and expression of adhesion molecules on the cellular surfaces, have been suggested to be important in the development of the systemic inflammatory response syndrome and multiple organ dysfunction syndrome[3]. In the present study, there was a significant decrease in endothelial barrier dysfunction after induction of AP in the pancreas, gut and lungs when animals were pretreated with a mast cell stabilizer (SCG). This indicates that endothelial permeability in AP is in part modulated by mast cells. The difference in effect in different organs may be explained by several factors. Tissue-dependent variations in plasma extravasation may exist in accordance with locoregional differences in endothelial barrier resistance[18,19], and phenotypic heterogeneity among mast cell populations together with differences in anatomical distribution of mast cells may contribute to the observed differences in effect[20,21]. Mast cell populations can exhibit significant heterogeneity in numbers, phenotype and function during the course of inflammatory or immune responses[22,23]. Mast cell stabilization in the present study did not completely abolish the increase in endothelial permeability. This is reasonable since endogenous substances other than those derived from mast cells are also involved in permeability changes. In addition, SCG does not necessarily stabilize the total mast cell population[10]. Alterations in the microvasculature may be due to the release of mediators in the immediate vicinity. Histamine and serotonin increase vascular permeability and histamine can cause vasodilatation, partial dissociation of the endothelium and initiate vascular changes early during the inflammatory process[24]. The major source of histamine is the mast cell and there was a significant decrease in plasma levels of histamine after mast cell stabilization in the present study. However, none of the antihistamines used was effective in restoring the impaired endothelial barrier permeability, implying the involvement of other mediators.

Endothelial cells also play a key role in the formation of an effective vascular barrier against various immune cells[25]; impairment of this barrier results in leucocyte recruitment, enhancement of the inflammatory response[26], and potentially serious tissue injury and concomitant organ dysfunction. In the present study, MPO levels were much higher in the pancreas than the colon (five times higher in animals with AP at 6 h). Therefore, the fulminant course of the disease might exceed the effect achieved by pretreatment with a single dose of SCG. In addition, mast cells might be involved during the initiation of injury, whereas other cells and their released mediators might dominate later during the course of the disease. The persistence of increased TNF-α levels indicate this ongoing process at later stages, at which time the role of other cells (neutrophils, macrophages and others) would be of greater importance. However, the leakage index demonstrates the involvement of mast cells at both early and late time points. This might be due to the presence of different pathways of endothelial permeability to macromolecules (albumin) or interaction with leucocytes. The findings emphasize the complexity of endothelial permeability modulation as suggested by Singh *et al.*[19]. The migration of inflammatory cells into an extravascular site thus requires a series of coordinated events.

Besides several cell-to-cell interaction phenomena, the presence of chemotactic agents is crucial to achieve leucocyte accumulation during the host inflammatory response[27]. Some of these chemokines (e.g. MCP-1) contribute to the initiation of inflammatory processes and recruitment of leucocytes since they are expressed at early time points[27–29]. Mast cells play a central role in the production of some chemokines in acute inflammation[30]. The increase in MCP-1 levels in the present study was reversed at an early time point after mast cell stabilization, implying that mast cells are involved mainly early in the initiation of AP and represent an important source of MCP-1 in acute inflammation. The lack of effect in the pancreas at the late time point studied may be explained by the fact that many other cell types (macrophages, endothelial cells and others) upon activation express MCP-1[31] and must be considered at this later stage.

Adhesion molecules are important in the trapping of circulating leucocytes to endothelial cells and concomitant transendothelial migration[32]. In the present study, the population of circulating leucocytes expressing adhesion molecules (PECAM-1 and L-selectin) was smaller in the saline-pretreated groups than in SCG-pretreated animals, indicating that the rest of this population was already engaged in either full adhesion to, or total migration through, endothelial cells.

In conclusion, activation of mast cells after induction of AP is involved in endothelial barrier dysfunction in both pancreatic and extrapancreatic organs/tissues. This effect is either direct or through the induction of leucocyte recruitment by upregulation of adhesion molecule expression and other inflammatory mediators.

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Original article

Extensive surgery for carcinoma of the gallbladder

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Background: The purpose of this study was to clarify the efficacy of, and define the indications for, extensive surgery for gallbladder carcinoma.

Methods: Between 1979 and 1994, 116 patients with gallbladder carcinoma underwent operation. Radical resection was performed in 80 patients.

Results: In 68 patients with stage III or IV disease, extensive resection including extended right hepatectomy ($n = 40$), pancreaticoduodenectomy ($n = 23$) and/or portal vein resection ($n = 23$) was employed to achieve complete tumour excision. The hospital mortality rate was 18 per cent. The postoperative 3- and 5-year survival rates were 44 and 33 per cent respectively in the patients with stage III disease ($n = 9$), and 24 and 17 per cent respectively in patients with stage IV (M_0) disease ($n = 29$). In contrast, the postoperative survival rate for the 30 patients with stage IV (M_1) disease (7 per cent at 3 years and 3 per cent at 5 years) was worse than that for patients with stage III and stage IV (M_0) disease ($P = 0{\cdot}009$ and $P = 0{\cdot}062$ respectively).

Conclusion: Radical resection should be undertaken for stage III and stage IV (M_0) gallbladder cancer. Although portal vein resection and/or pancreaticoduodenectomy did not contribute to long-term survival, better survival was obtained than that for the unresected patients.

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Introduction

Although extensive surgery including major hepatic resection, pancreaticoduodenectomy and/or combined portal vein resection for advanced gallbladder carcinoma has been reported recently[1–3], its efficacy and long-term outcome are unknown. Since 1979, the strict policy in this unit has been to employ radical surgery[4–6]. The purpose of the present article was to appraise the results of this surgical treatment and to clarify the indications for extensive surgery for advanced gallbladder carcinoma.

Patients and methods

Between 1979 and 1994, 116 patients with gallbladder carcinoma underwent surgery. During this period, a surgical approach aimed at achieving a cure was employed in all patients with gallbladder carcinoma unless they had extensive distant metastasis or involvement of the proper and/or left hepatic artery (*Table 1*). Informed consent was obtained before treatment.

Distant metastasis was classified into extensive and limited metastasis, the latter being defined as hepatic or peritoneal nodules confined to areas near the gallbladder and lymph node metastasis in the abdominal para-aortic area. Limited distant metastases were resected with the primary tumour. *En bloc* resection of macroscopically involved neighbouring organs such as the duodenum, pancreas and portal vein was performed, so frozen sections were not used routinely except for hepatic or peritoneal nodules. Prophylactic resection of surrounding organs without apparent tumour invasion was not employed. Regional lymphadenectomy was performed routinely. The para-aortic lymph nodes were dissected extensively in most patients, except those with intramucosal cancer. The surgical plan was based on the results of preoperative imaging and modified according to the intraoperative findings. All 70 patients with obstructive jaundice underwent percutaneous transhepatic biliary drainage before operation. They were operated on after the serum bilirubin level had decreased below 2 mg/dl.

All resected specimens collected from 1979 were examined microscopically and restaged according to the Union Internacional Contra la Cancrum (UICC) tumour node metastasis (TNM) classification of 1997[7]. There were five patients with stage I, seven patients with stage II, nine patients with stage III and 95 patients with stage IV gallbladder carcinoma. Most of the patients with stage IV disease had initially been diagnosed as having irresectable tumours at another institute. All of the patients with stage I–III tumours, and 59 (62 per cent) of the 95 patients with stage IV disease underwent radical resection that secured negative resection margins with no residual tumour. Limited distant metastases were confirmed microscopically in the resected specimens in 30 of the 59 patients with stage IV disease who underwent radical resection (stage IV (M_1)), but not in the other 29 patients (stage IV (M_0)). In the 30 patients with stage IV (M_1) disease, limited distant metastases were found in the para-aortic lymph nodes (n = 24), liver (n = 10) and peritoneum (n = 3). The remaining 36 patients with stage IV disease underwent palliative surgery. Grading of tumours was also performed according to the UICC classification[7]. Among the 12 patients with stage I or II disease, 11 had well differentiated (G1) and one had moderately differentiated (G2) gallbladder carcinoma. Among the 68 patients who underwent radical resection for stage III or IV disease, four, 43 and 21 patients had G1, G2 and G3 (poorly differentiated) carcinoma respectively. Neither adjuvant chemotherapy nor radiotherapy was administrated.

The survival rates after surgery were calculated using the Kaplan–Meier method. Statistical comparisons of survival were performed with the log rank test.

Results

Surgical procedures

In the patients with stage I or II gallbladder carcinoma, curative resection was accomplished by simple cholecystectomy (n = 6) or radical cholecystectomy including resection of the adjacent liver parenchyma and regional lymph nodes (n = 6). One patient underwent pancreaticoduodenectomy because of a concomitant benign tumour (intraductal papillary mucinous tumour) of the pancreatic head. In the 68 patients who underwent radical resection for stage III or IV disease, radical cholecystectomy with extended right hepatectomy (n = 40; 59 per cent), pancreaticoduodenectomy (n = 23; 34 per cent) and/or portal vein resection (n = 23; 34 per cent) was necessary for complete removal of tumour (*Fig. 1*). Palliative surgery included exploratory laparotomy (n = 7), bypass operation (n = 15) and palliative resection (n = 14) that resulted in macroscopic and/or microscopic residual tumours or positive resection margins.

Morbidity and mortality rates

Hospital mortality calculations included all deaths within and over 30 days of operation (*Table 2*). There were no deaths among patients with stage I–III disease. The morbidity and mortality rates for the 59 patients with stage IV tumours who underwent radical resection were 51 and 20 per cent respectively. Six patients with a stage IV (M_0) tumour died in hospital 3, 10, 16, 20, 25 and 49 days after operation, and six patients with stage IV (M_1) disease also died during their hospital stay 8, 8, 18, 42, 53 and 75 days after surgery. All 12 hospital deaths occurred after extended right hepatectomy (*Fig. 1*). Obstructive jaundice was also a significant determinant of hospital death (P = 0·005, χ^2 test). Postoperative hepatic failure developed after extended right hepatectomy for a cholestatic liver and was the most common cause of death (eight of 12 deaths). The patients who died from hepatic failure did not have ongoing cholangitis. Although the mortality rate was high after radical resection for patients with stage IV disease, it was lower than that (33 per cent) after palliative surgery for patients with stage IV disease. The main cause of death after palliative surgery was tumour progression rather than postoperative complications.

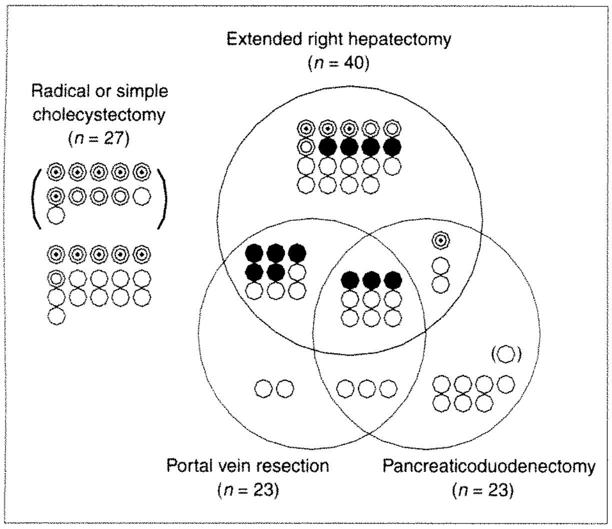
Table 1 Guidelines employed for surgical treatment of gallbladder carcinoma

Preoperative and/or intraoperative findings	Procedure of choice
Direct hepatic invasion	Cholecystectomy plus resection of the adjacent liver depending on the degree of hepatic invasion (varying from wedge resection to extended right hepatectomy)
Involvement of the hepatic hilum and the right portal pedicle	Extended right hepatectomy plus caudate lobectomy
Subserosal invasion at the neck of the gallbladder or evident nodal metastasis in the hepatoduodenal ligament	*En bloc* resection and reconstruction of the bile duct
Invasion of the duodenum and/or the head of the pancreas	Pancreaticoduodenectomy
Invasion of the portal vein	*En bloc* resection and reconstruction of the portal vein
Invasion of the other neighbouring organs (colon, stomach, abdominal wall, etc.)	*En bloc* resection
Evident and/or occult nodal metastasis	Routine dissection of the regional lymph nodes using a skeletonization technique and para-aortic lymphadenectomy
Hepatic metastasis or peritoneal seeding confined to areas near the gallbladder	*En bloc* resection

Postoperative survival

All of the 12 patients with stage I or II disease were alive without recurrence at the last follow-up, apart from three patients who died from causes other than the gallbladder cancer 3, 44 and 152 months after surgery (*Fig. 2*). Six patients have survived for more than 5 years (*Fig. 1*).

Of the 68 patients with stage III or IV disease who underwent radical resection, 13 have survived for more than 3 years, of whom nine have survived for more than 5 years (*Fig. 1*, *Table 3*). At the last follow-up, seven 5-year survivors were disease free. Obstructive jaundice was not a prognostic determinant; seven patients presenting with jaundice have survived for more than 3 years, of whom four have survived for more than 5 years. The presence of limited distant metastases had a negative impact on survival (*Fig. 2*). There were some long-term survivors among the group of patients who underwent extended right hepatectomy (*Fig. 1*). However, there was only one long-term survivor among the group of patients who underwent portal vein resection or pancreaticoduodenectomy. The postoperative 1- and 2-year survival rates were 39 and 13 per cent respectively in patients who underwent portal vein resection, and 48 and 17 per cent respectively in patients who had pancreaticoduodenectomy. These survival rates were significantly better than those of the 22 unresected patients, all of whom died within 1 year after operation ($P = 0{\cdot}014$ and $P < 0{\cdot}001$ respectively).



◉ 5-year survivors (*n* = 15)

◎ 3-year survivors who died (*n* = 5) or were lost to follow-up (*n* = 2) within 5 years after surgery

● Patients who died in hospital after surgery (*n* = 12)

○ Patients who were discharged and died (*n* = 44) or were lost to follow-up (*n* = 2) within 3 years after surgery

Fig. 1 Surgical procedures and outcome in 80 patients who underwent radical resection. Symbols in parentheses represent patients with stage I or II disease

There was no statistically significant difference ($P = 0{\cdot}294$) between the survival rates for stage III (44 per cent at 3 years and 33 per cent at 5 years) and stage IV (M_0) (24 per cent at 3 years and 17 per cent at 5 years) disease (*Fig. 2*, *Table 2*). These survival rates were significantly worse than those for the patients with stage I or II disease ($P = 0{\cdot}024$ and $P < 0{\cdot}001$ respectively). However, they were better than the survival rates for patients with stage IV (M_1) disease ($P = 0{\cdot}009$ and $P = 0{\cdot}062$ respectively) (*Fig. 2*). All of the patients who underwent palliative surgery died within 1 year of operation despite various types of chemotherapy. The survival rate for this group was significantly worse than that for patients with stage IV (M_1) disease who underwent radical surgery ($P = 0{\cdot}004$) (*Fig. 2*).

Sites of tumour recurrence

There was no tumour recurrence in patients with stage I or II disease. Of the 68 patients who underwent radical resection for stage III or IV disease, 48 patients died from tumour recurrence. Two of them died more than 5 years after surgery; four died between 3 and 5 years after operation. Sites of tumour recurrence were identified by

Table 2 Results of operation in 116 patients with gallbladder carcinoma

Stage	No. of patients	Operative morbidity (%)	Hospital mortality (%)	Survival rate (%)			Median survival (months)
				1 year	3 years	5 years	
Radical resection							
I and II	12	25	0	92	92	80	—
III	9	33	0	78	44	33	22·2
IV (M_0)	29	41	21	52	24	17	12·1
IV (M_1)	30	60	20	37	7	3	6·6
Palliative operation							
IV	36	42	33	0	0	0	4·7

autopsy, relaparotomy or diagnostic imaging in 40 of the 48 patients. Abdominal tumour recurrence included seeding metastases in 13 patients, hepatic metastases in 12 patients, lymph node metastases (mostly para-aortic nodes) in ten patients and local recurrence in nine patients. Sites of recurrence outside the peritoneal cavity were the neck and mediastinum in five patients, the lung in five patients and the bone in three patients.

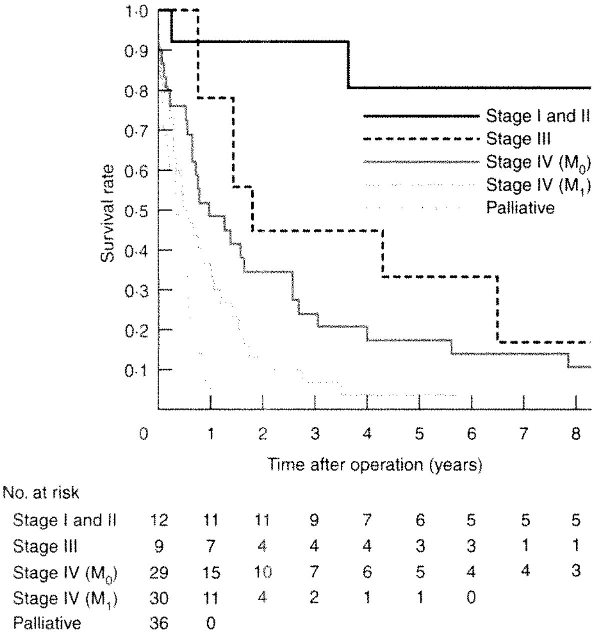


Fig. 2 Postoperative survival of patients undergoing radical resection for gallbladder cancer according to Union Internacional Contra la Cancrum staging and patients undergoing palliative operation. $P = 0{\cdot}024$ (stage I and II *versus* stage III); $P = 0{\cdot}294$ (stage III *versus* stage IV (M_0)); $P = 0{\cdot}062$ (stage IV (M_0) *versus* stage IV (M_1)); $P = 0{\cdot}004$ (stage IV (M_1) *versus* palliative) (log rank test)

Discussion

Satisfactory results were achieved by simple or radical cholecystectomy in patients with stage I or II disease. Extensive surgery is not necessary in these patients[8–12]. However, poor outcomes have also been reported using this approach[13,14]. These poor results might have been due to the inclusion of patients with stage III or IV disease with occult nodal metastases, because routine dissection and histological examination of the lymph nodes had not been performed.

In contrast, the results of surgical treatment of stages III and IV gallbladder carcinoma have been reported to be extremely poor[8,13,15]. Recently, the results have improved as a result of the introduction of extensive resection (*Table 3*)[2,3,16–22], including *en bloc* resection of involved organs. A high resection rate of 65 per cent in patients with stage III or IV disease was achieved in the present study, in which extensive surgery was based on precise preoperative evaluation of tumour extension. Although the hospital mortality rate for patients with stage III or IV disease who had radical resection was high (18 per cent), it was lower than that (33 per cent) of patients who underwent palliative surgery. High mortality rates (20–33 per cent) have been reported in some previous studies of radical surgery[2,8,14,18], but not in others[20,22,23]. All 12 patients in this study who died after operation had undergone extended right hepatectomy. The majority ($n = 8$) died from postoperative hepatic failure; all of them had

Table 3 Reports of extensive surgery and long-term survival in patients with stages III and IV gallbladder cancer

					No. of long-term survivors			
		No. of extensive resections			Stage III		Stage IV	
Reference	Year	ERH	PD	PVR	3 years	5 years	3 years	5 years
Gall *et al.*[16]	1991	1			2	1	1	
Todoroki *et al.*[17]	1991	2	4				1	
Chijiiwa and Tanaka[18]	1994		3		6	4	1	
Ruckert *et al.*[19]	1996	7				1		1
Bartlett *et al.*[20]	1996	12					2	
Okamoto *et al.*[21]	1996	5	9			3		1
Miyazaki *et al.*[2]	1996	21	7	7			4	2
Tsukada *et al.*[3]	1996	18	22			10		2
Paquet[22]	1998	7				4		2
Present study	2002	40	23	23	4	3	9	6

ERH, extended right hepatectomy; PD, pancreaticoduodenectomy; PVR, portal vein resection undergone major hepatectomy in the presence of liver damage due to obstructive jaundice, which has rarely been reported in other studies. Miyazaki *et al.*[2] used major hepatectomy in patients with cholestasis and also reported hepatic failure as the most common cause of postoperative death. Extended right hepatectomy of the cholestatic liver carries a high risk of postoperative hepatic failure even if the preoperative serum bilirubin level has fallen to normal by percutaneous transhepatic biliary drainage, and laboratory evaluation (such as indocyanine green excretion and prothrombin tests) shows almost normal liver function. In the present series, 37 of the 40 patients who underwent extended right hepatectomy had cholestasis. To prevent postoperative hepatic failure, preoperative portal vein embolization is now performed in all patients in whom a major hepatic resection in a cholestatic liver is planned[24–26], although the role of the embolization in reducing the postoperative mortality rate has not yet been fully evaluated.

Extensive surgery has been reported to result in long-term survival in selected patients with stage IV gallbladder carcinoma (*Table 3*). In the present series, there were more long-term survivors than in any other report. Survival outcome analysis using two patient groups according to the UICC subgrouping, stage IVA ($n = 17$) and IVB ($n = 42$), did not show a statistically significant difference; however, a borderline significant difference in survival was noted between two patient groups classified simply by whether limited distant metastases were absent or present, stage IV (M_0) ($n = 29$) and IV (M_1) ($n = 30$) (*Fig. 2*). The presence of limited distant metastases was associated with worse survival. Thus extensive surgery should be performed in patients with stage III or stage IV (M_0) gallbladder carcinoma. Based on the present results, radical resection has been abandoned when gallbladder carcinoma is associated with hepatic metastasis, peritoneal seeding and/or para-aortic lymph node metastasis, even if they are confined to areas near the gallbladder. Radical resection with portal vein resection and/or pancreaticoduodenectomy should be undertaken only when survival for 1 year or more and an improvement in quality of life are possible. To identify limited distant metastases before radical surgery, it may be necessary to utilize more reliable diagnostic procedures such as laparoscopic exploration[27] or routine sampling of para-aortic nodes[6].

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Original article

Effects of experimental lower-limb ischaemia–reperfusion injury on the mesenteric microcirculation

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Background: Ischaemia–reperfusion (I-R) of the leg is associated with functional and structural changes in the intestine. This study assessed whether acute hind-limb I-R in rats induced a reduction in perfusion and/or signs of an inflammatory response in the intestine.

Methods: Rats were subjected to 2 h of unilateral hind-limb ischaemia followed by 2 h of reperfusion (I-R group, $n = 9$) or to a sham procedure (control group, $n = 9$). Mesenteric microvascular diameters, red blood cell velocity, blood flow and leucocyte–vessel wall interactions during reperfusion were measured using intravital microscopy.

Results: Blood pressure and heart rate decreased from 30 min of reperfusion onwards in the I-R group compared with controls. From 15 min after the start of reperfusion, mesenteric arteriolar and venular red blood cell velocity and blood flow decreased by 40–50 per cent. Microvascular diameters and leucocyte–vessel wall interactions did not change.

Conclusion: Restoration of blood flow to an acutely ischaemic hind limb led to a significant decline in the splanchnic microcirculatory blood flow. There were, however, no signs of an early inflammatory response in the gut.

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Introduction

Ischaemia–reperfusion (I-R) injury of the leg is a common clinical event that occurs following surgery for trauma, arterial thromboembolism, cardiac surgery or aortic aneurysm. In addition to local effects of reperfusion (e.g. massive oedema and muscle necrosis), limb I-R injury may also lead to systemic complications such as multiple organ failure[1,2]. Multiple organ failure is associated with a mortality rate of 35–50 per cent and remains, despite advances in the management of critically ill patients, the leading cause of death in the intensive care unit[3].

The pathophysiological mechanisms by which remote I-R injury promotes multiple organ failure are still unclear. Experimental evidence suggests that the gut is an important mediator in this process. It has been demonstrated in rats that reperfusion of ischaemic hind limbs is associated with a reduction of intestinal mucosal thickness and an increase in intestinal permeability, as well as an increase in systemic endotoxin concentration[4,5]. These studies indicate that hind-limb I-R induces a loss of the intestinal barrier function, with subsequent translocation of endotoxin from the gut. This sequence of events may activate cellular and humoral host responses, resulting in a systemic inflammatory response that finally culminates in multiple organ failure[6–9].

The nature of the link between reperfusion of an ischaemic leg and the intestinal changes remains to be elucidated. Disruption of the intestinal barrier may be caused by diminished intestinal perfusion[10]. Alternatively, inflammatory mediators that are released into the systemic circulation upon reperfusion of the ischaemic leg may induce intestinal changes directly or, alternatively, via infiltration of leucocytes.

The aim of this study was to assess whether hind-limb I-R induces a reduction in intestinal blood flow and/or an increase in leucocyte–vessel wall interactions in intestinal microvessels. Haemodynamic variables and leucocyte–vessel wall interactions in mesenteric microvessels were therefore quantified in a previously characterized rat model of hind-limb I-R[11].

Materials and methods

Animal preparation

Experiments were approved by the local ethics committee on the use of laboratory animals. Eighteen male Lewis rats with a median weight of 329 (range 280–360) g were used. Experiments were performed according to a standard protocol. Animals were assigned randomly before the experiments to one of the experimental groups using a computer-generated randomization schedule. Anaesthesia was induced by an intraperitoneal bolus injection of sodium pentobarbital 6·6 mg per 100 g body-weight (Nembutal; Sanofi Sante, Maassluis, The Netherlands). Anaesthesia was maintained by continuous infusion of sodium pentobarbital (2·6 mg per 100 g body-weight per h) via a catheter (polyethylene (PE) 10) in the left femoral vein, starting 1 h after the bolus injection. A second catheter (PE 10) was placed in the left femoral artery and connected to an external pressure transducer (Uniflow; Baxter, Uden, The Netherlands) for measurement of arterial blood pressure and heart rate (HR). To prevent blockage of the tip, this catheter was continuously perfused with saline (0·9 per cent sodium chloride) at a rate of 1 ml/h. Mean arterial pressure (MAP) and HR were recorded continuously on a computer using a home-made data acquisition system (Technical Department, Cardiovascular Research Institute, Maastricht). The body temperature of the rat was maintained at 37°C throughout the experiment by means of an infrared heating lamp controlled by a thermoanalyser system (Hugo Sack Elektronic, Hugstetten, Germany) that was connected to a rectal probe.

Experimental protocol

After a 15-min acclimatization period following the surgical procedure, the anaesthetized rats were randomized to a hind-limb I-R group ($n = 9$) or to a control group ($n = 9$). In the I-R group, ischaemia of the right hind limb was induced by inflating a cuff placed around the thigh at 300 mmHg. This method has previously been established to induce complete hind-limb ischaemia, as verified by demonstrating no flow in all vessels observed in the toenail fold using intravital videomicroscopy[11]. In the control group, the cuff was placed but not inflated. The total duration of ischaemia was 2 h, followed by 2 h of reperfusion. To prevent local hypothermia, the experimental hind limb was positioned inside a water-perfused heating pad kept at 37°C. At the end of the protocol, rats were killed by an overdose of pentobarbital.

Mesenteric preparation and intravital videomicroscopy

Some 45 min before the end of the ischaemic or sham interval, an incision was made in the left flank and the distal ileum with its accompanying mesentery was exteriorized. The mesentery was spread over a siliconized glass plate mounted in the electrically heated table (37°C) of an intravital microscope. The mesentery was superfused continuously with buffered Tyrode's solution (37°C, pH 7·4) saturated with a mixture of nitrogen (95 per cent) and carbon dioxide (5 per cent). The ileum was kept moist with overlying wet gauze. Care was taken to minimize manipulation of the intestinal tissue, and the procedure was completed within 15 min.

The mesenteric preparation was allowed to stabilize for 30 min after exposure until the start of the reperfusion phase. The mesentery was transilluminated with a 60-W tungsten lamp, and microvessels were observed with a Leitz ×25 salt-water immersion objective (numerical aperture 0·6) using a Leitz intravital microscope adapted to telescopic imaging (Leitz, Wetzlar, Germany). Images were projected into a charge-coupled device camera (Hamamatsu Photonics, Hamamatsu City, Japan), displayed on a monitor screen (effective size 111 × 144 μm) and stored on videotape (SuperVHS; Panasonic, Osaka, Japan) for off-line analysis. For on-line measurement of red blood cell velocity (RBCV) a bidirectional optical three-stage prism grating system was used[12].

In the mesentery of each animal one arteriole (diameter range 9–23 μm) and one venule (diameter range 14–29 μm) were selected. Just before the start of hind-limb reperfusion, before any blood had left the ischaemic hind limb, pre-reperfusion measurements were performed: RBCV was measured and a 2-min video recording was made of each selected vessel. After the pre-reperfusion recordings, reperfusion of the hind limb was initiated by deflating the thigh cuff. Video recordings and RBCV measurements were made at 15, 30, 60, 90 and 120 min after hind-limb reperfusion. Haematocrit and systemic leucocyte counts were assessed in blood sampled from the femoral artery (0·25 ml) before reperfusion, as well as at 60 and 120 min after the start of reperfusion. For systemic leucocyte counts, 20 μl blood was collected in Türk's solution (0·2 mg gentian violet in 1 ml glacial acetic acid 6·25 per cent). Counts were subsequently performed in a Bürker chamber.

Experimental variables

All microvascular and leucocyte–endothelial interaction data were analysed off-line by an investigator who was blinded with respect to randomization. Leucocytes were considered to be rolling if they could be seen moving slowly along the venular wall by eye, at a velocity that was at least an order of magnitude slower than that of free-flowing blood cells. The degree of leucocyte rolling was quantified by counting the number of rolling leucocytes passing an imaginary line perpendicular to the venular axis per minute[13,14]. The total number of interacting leucocytes was assessed as an overall parameter of leucocyte–vessel wall interaction, because it included the number of both adherent and rolling leucocytes as well as the velocity of the latter. This variable was assessed by counting the total number of visible (i.e. rolling or adherent) leucocytes in a vessel segment 100 µm in length; the data obtained from two randomly frozen video frames were averaged[15,16].

Luminal diameters of arterioles and venules were measured using a video image shearing device[15,17]. To reduce measurement bias, the diameter was measured at two nearby sites within the selected vessel segment; the mean was taken as the actual diameter. RBCV was measured online (see above). To obtain actual mean RBCV values (mRBCV), the measured velocity was divided by a conversion factor[18] of 1·1. Blood flow (Q) was calculated using the mRBCV and diameter (D) data, according to the following equation:

$$Q = \pi \times (D/2)^2 \times \text{mRBCV}$$

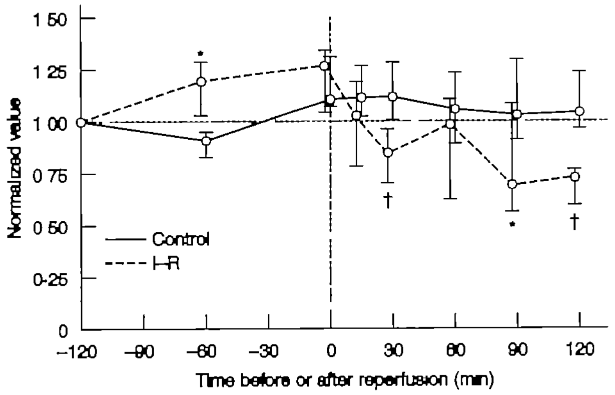
Data analysis

Because of their asymmetrical distribution, data were presented as median (interquartile range). To enable comparisons between groups, data were normalized to the pre-reperfusion values. The Mann–Whitney *U* test was used to compare data from ischaemic and control groups at each timepoint. The Wilcoxon signed ranks test was used to compare changes during the course of the experiment with pre-reperfusion values within each group. Spearman's rho was calculated to assess any relationship between data groups. $P < 0.05$ was considered statistically significant.

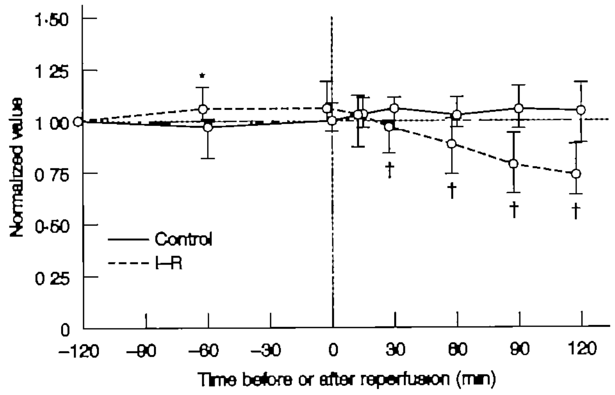
Results

Systemic variables

Pre-reperfusion MAP and HR did not differ significantly between the control (100 mmHg and 350 beats per minute (b.p.m.) respectively) and the I-R (99 mmHg and 375 b.p.m.) groups. In the control group HR and MAP remained constant during the whole protocol (*Fig. 1*). In the I-R group these variables were significantly lower than those in the control group ($P < 0.05$) from 30 min after the start of reperfusion onwards.



a Mean arterial pressure



b Heart rate

Fig. 1 a Mean arterial blood pressure and b heart rate normalized to pre-reperfusion values. I-R, ischaemia–reperfusion. *$P < 0.05$, †$P < 0.01$ *versus* control group (Mann–Whitney *U* test)

Pre-reperfusion systemic leucocyte counts were similar in both groups and did not increase significantly over the course of the experiment, with mean values ranging from 6·0 to 6·8 × 10^6 leucocytes/ml. Before reperfusion no significant difference was detected in haematocrit values between control and I-R groups (0·43 and 0·43 respectively). After 2 h of reperfusion the haematocrit was significantly higher in the I-R group compared with that in the control group (0·49 *versus* 0·45; $P < 0.05$).

Local haemodynamic variables

Mean pre-reperfusion arteriolar and venular diameters were similar in the control and I-R groups (*Table 1*). Data from subsequent intervals were therefore normalized to pre-reperfusion values. In both groups no significant change in arteriolar or venular diameter was observed throughout the experimental protocol (data not shown).

Table 1 Pre-reperfusion values of microvascular variables in control and ischaemia–reperfusion groups assessed immediately before reperfusion of the hind limb in rats

	Control	I-R
Diameter (µm)		
Arteriole	13·5 (10·7–15·1)	13·0 (11·4–15·2)
Venule	19·0 (17·8–20·7)	21·7 (19·1–23·3)
mRBCV (mm/s)		
Arteriole	2·9 (2·0–8·0)	2·4 (2·1–6·1)
Venule	1·2 (1·0–2·4)	0·8 (0·6–1·2)
Blood flow (nl/s)		
Arteriole	0·5 (0·2–1·6)	0·4 (0·2–0·8)
Venule	0·4 (0·3–0·7)	0·3 (0·2–0·4)

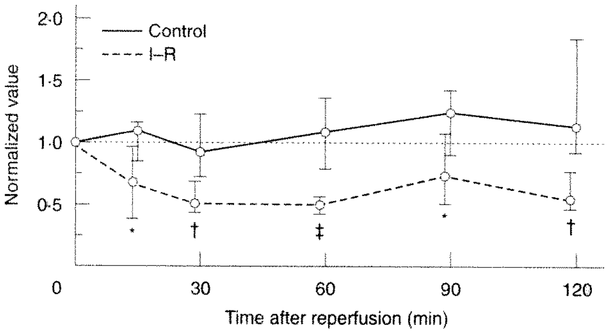
Values are median (interquartile range). I-R, ischaemia–reperfusion; mRBCV, mean red blood cell velocity

Pre-reperfusion mRBCV in the I-R group did not differ significantly from that in the control group (*Table 1*). Within the control group there were no significant changes in mRBCV during the protocol; median values ranged from 2·9 to 3·7 mm/s (*Fig. 2*). In contrast, in the I-R group arteriolar mRBCV decreased significantly by about 40 per cent ($P < 0·05$) during the first 15 min after the start of reperfusion and remained more or less constant during the 2 h of reperfusion. A similar pattern was found in the venules. Pre-reperfusion venular mRBCV values were similar in both groups (*Table 1*). In the control group venular mRBCV did not change significantly; however, venular mRBCV decreased significantly ($P < 0·05$), by about 50 per cent in the I-R group from 15 min after the start of reperfusion.

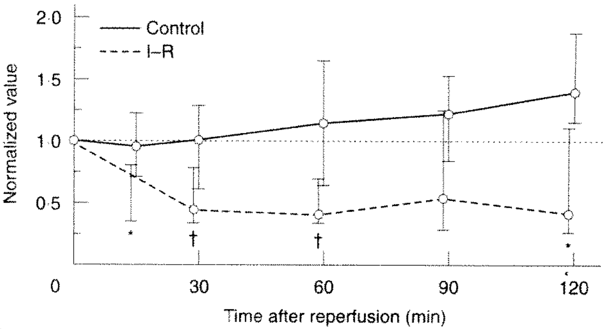
As vascular diameters remained constant throughout the experiments, blood flow followed a pattern similar to that of mRBCV in both arterioles (*Fig. 2*) and venules. In the control group arteriolar and venular blood flow remained constant, and even tended to increase towards the end of the experiment. In contrast, in the I-R group both arteriolar and venular blood flow decreased significantly during the first 30 min of reperfusion to approximately 50 per cent of pre-reperfusion values, and remained constant thereafter. The decrease in arteriolar blood flow correlated significantly with the decrease in MAP, indicating that at least part of the observed changes in arteriolar flow resulted from the decrease in systemic blood pressure ($r_s = 0·40$, $P < 0·01$).

Leucocyte–vessel wall interactions

Leucocyte–vessel wall interactions were observed only in mesenteric venules, never in arterioles. Before reperfusion, both the number of rolling leucocytes and the total number of interacting leucocytes did not differ significantly between the control group (52 per min and 3 per 100 µm respectively) and the I-R group (44 per min and 4 per 100 µm). No significant changes in the number of rolling or interacting leucocytes were observed during the course of the experiment in either of the groups (*Fig. 3*).



a Arteriolar red blood cell velocity

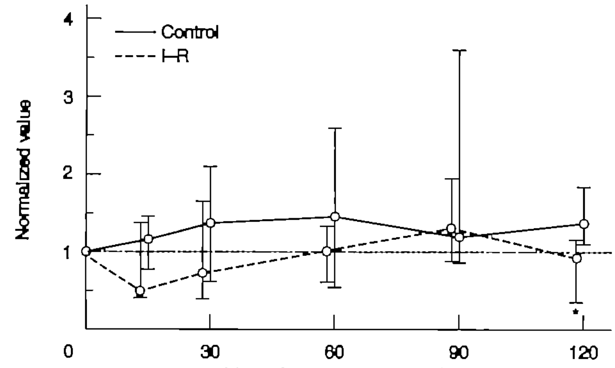


b Arteriolar blood flow

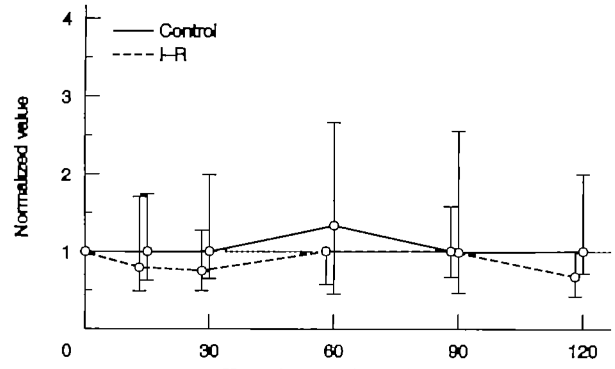
Fig. 2 a Mesenteric red blood cell velocity and **b** blood flow normalized to values obtained before the start of reperfusion. I-R, ischaemia–reperfusion. *$P < 0·05$, †$P < 0·01$, ‡$P < 0·001$ *versus* control group (Mann–Whitney U test)

Discussion

Reperfusion of one or both legs following acute ischaemia may lead to multiple organ failure. Clinical, as well as experimental, evidence indicates that the gut is an important mediator in the systemic complications of I-R injury. It has been suggested that the intestinal changes following limb I-R are caused by a reduction in intestinal perfusion and/or infiltration of leucocytes into the intestinal tissue. This study investigated the effect of unilateral hind-limb I-R in the rat on haemodynamic variables and leucocyte–vessel wall interactions in the mesenteric microcirculation. Reperfusion of the hind limb following 2 h of ischaemia resulted in a severe reduction in blood flow in mesenteric arterioles and venules of 40–50 per cent. However, no changes in leucocyte–vessel wall interactions were observed.



a No. of rolling leucocytes



b Total no. of interacting leucocytes

Fig. 3 a Number of rolling leucocytes and b total number of interacting leucocytes normalized to values obtained before the start of reperfusion. I-R, ischaemia–reperfusion. $^*P < 0{\cdot}05$ *versus* control group (Mann–Whitney *U* test)

The reduction in mesenteric blood flow that accompanied hind-limb reperfusion was likely to reflect a decrease in intestinal perfusion. This decline in mesenteric microvascular blood flow correlated significantly with a reduction in arterial blood pressure, although the decrease in mesenteric blood flow exceeded the decline in blood pressure. There was a significant decrease in MAP at the start of hind-limb reperfusion, which persisted throughout the 2 h of reperfusion. This decrease in arterial pressure may have been the direct result of hypovolaemia due to the development of oedema in the leg as well as in distant organs[19]. Reperfusion of ischaemic tissue induces the release of inflammatory mediators that may cause irreversible endothelial cell damage, resulting in capillary leakage and oedema formation[20–22]. In an attempt to correct for such loss, saline was administered directly after the start of reperfusion in a pilot group of four rats (data not shown). However, saline replacement at a near-maximal supplementation rate of 4 ml/h did not prevent the decrease in arterial pressure or improve the mesenteric blood flow. Moreover, fluid replacement did not decrease the haematocrit level, indicating that the saline leaked out of the vascular system immediately. These results suggest that the fall in systemic blood pressure and the resulting decrease in intestinal blood flow during reperfusion were at least partly related to a reduction in effective circulating volume due to capillary leakage. However, a larger group of experiments is required to confirm these preliminary observations.

In this study there were no changes in leucocyte–vessel wall interactions in the mesenteric venules throughout the experimental protocol. These findings are in contrast with the increase in the rolling and adherence of leucocytes in the mesenteric microcirculation that was reported recently in a rat model of bilateral hind-limb I-R[23]. This difference might be explained by the more severe injury in the model of Sobral do Rosario *et al.*[23], in which bilateral ischaemia was induced for 4 h, in contrast to 2 h of unilateral ischaemia in the present model. It has been speculated that oxygen free radicals and proinflammatory mediators are released into the systemic circulation during reperfusion, leading to the generation of chemoattractants. Subsequent recruitment of activated neutrophils, which is accompanied by interactions between leucocytes and the venular endothelium, may result in tissue damage in distant organs. Indeed, increased systemic expression of the leucocyte adhesion molecules P-selectin[24] and intercellular adhesion molecule 1[25] has been reported following remote I-R injury and may play an instrumental role in the process of leucocyte sequestration. However, experimental studies with regard to this subject have provided conflicting evidence. It has been demonstrated that neutrophils contribute to lung injury[26]. On the other hand, morphological changes in the intestine in response to 3 h of bilateral hind-limb ischaemia followed by 2 h of reperfusion were not associated with neutrophil infiltration into the intestinal tissue[5], in line with the findings in the present study.

This study demonstrated *in vivo* that reperfusion of ischaemic tissue well away from the gut caused a blood flow reduction in the splanchnic circulation. This finding provides a mechanism for the previously observed morphological and functional changes in the intestine in response to I-R of the leg[4,5]. In animal models of burn injury, haemorrhagic shock and endotoxaemia, diminished intestinal perfusion was associated with increased epithelial permeability[10,27,28]. The epithelial lining is an important constituent of the intestinal barrier to the penetration of antigens present in the intestinal lumen. Consequently, a loss of mucosal barrier function may result in the translocation of bacteria and (endo)toxin from the lumen into gut wall, as well as into the systemic circulation[29,30]. Local and systemic activation of the inflammatory system may result in the production of cytokines, initiating a systemic inflammatory response that culminates in multiple organ failure[7–9,31,32].

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Short note

Comparison of colour Doppler ultrasonography, ascending phlebography and clinical examination in the diagnosis of incompetent calf perforating veins

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Introduction

Colour Doppler ultrasonography (CDS) has become a major diagnostic tool in preoperative evaluation of patients with varicose veins. This study compared the ability of CDS, ascending phlebography and clinical examination in defining whether a perforating vein was incompetent as an aid to further operative planning.

Patients and methods

Fifty patients (63 legs) of mean age 51 years with typical signs of chronic venous insufficiency, classified Clinical, Etiologic, Anatomic and Pathologic 4[1], were entered into the study. Perforator incompetence was diagnosed at clinical examination if a palpable fascial gap or a blow-out phenomenon was verified.

A 7·5-MHz probe with an integrated colour Doppler (Versa Pro™; Siemens, Erlangen, Germany) was used for high-resolution ultrasonographic imaging. Outward flow of more than 0·5 s on Valsalva's manoeuvre and on compression of the distal parts of the calf was characteristic of venous incompetence[2].

At ascending phlebography typical signs of incompetence were outward flow of contrast material on Valsalva's manoeuvre, contrasting of just a single vein (instead of the typical twin veins) and an angle of origin from the deep venous system of more than 60° (*Fig. 1*).

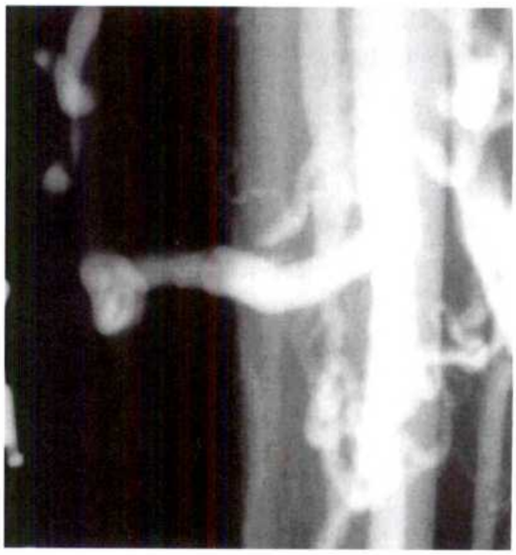

Fig. 1 Ascending phlebography of incompetent perforating vein, showing contrasting of a single vein with an angle of origin of more than 60°

Subfascial endoscopic perforator surgery (SEPS) was carried out with the use of an endoscope (ETB, Berlin, Germany) for thermic dissection. At operation a perforating vein was defined as incompetent if a single dilated vein that showed retrograde flow on calf compression was found passing through the fascia (*Fig. 2*).

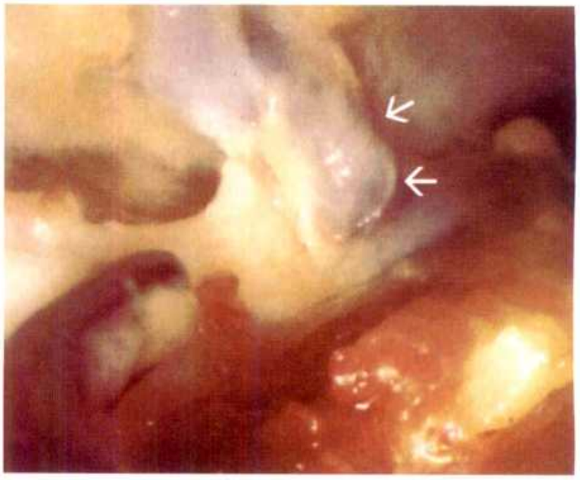

Fig. 2 Incompetent calf perforating vein (arrows) during subfascial endoscopic perforator surgery; a single dilated perforating vein passing the deep fascia

In all examinations incompetent calf perforators were defined as Cockett 1–3 according to their distance from the sole of the foot. Cockett 1 was found at 6–9 cm, Cockett 2 at 13–16 cm, and Cockett 3 at 19–22 cm. All examiners and the operating surgeon were blinded to the results of the other examinations.

Differences in values of sensitivity and specificity were analysed by the use of McNemar's test for matched pair proportions.

Results

The overall sensitivity and specificity of the evaluation of Cockett I–III perforators with CDS was 80 and 74 per cent

Table 1 Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of combinations of colour Doppler ultrasonography, ascending phlebography and clinical examination in preoperative evaluation of incompetent calf perforating veins

	Cockett's perforator	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Clinical examination and CDS	I	78	61	68	73	70
	II	90	62	90	62	84
	III	94	33	86	57	82
	Mean I–III	87	52	81	64	79
Clinical examination and phlebography	I	69	55	61	63	62
	II	82	58	89	44	78
	III	92	42	87	56	82
	Mean I–III	81	52	79	54	74
Clinical examination, CDS and phlebography	I	78	52	62	70	65
	II	90	50	88	54	82
	III	94	33	86	57	82
	Mean I–III	88	45	79	60	77

PPV, positive predictive value; NPV, negative predictive value; CDS, colour Doppler ultrasonography

respectively. CDS was more sensitive than ascending phlebography (66 per cent) ($P < 0{\cdot}01$) and the specificity of CDS was significantly higher than that of clinical examination (60 per cent) ($P < 0{\cdot}05$). Clinical examination also proved to be more sensitive (79 per cent) than ascending phlebography (66 per cent) ($P < 0{\cdot}01$). Differences in the specificity of CDS and ascending phlebography were not statistically significant.

Sensitivity was improved to 87 per cent by combining clinical examination and CDS (*Table 1*).

Discussion

The sensitivity of CDS proved to be superior to that of ascending phlebography in imaging all three Cockett perforators with a mean of 80 per cent. Although a combination of clinical examination with CDS led to further improvement in sensitivity over either technique alone, the addition of ascending phlebography yielded no further advantage over clinical examination and CDS (*Table 1*). Therefore it does not seem favourable to perform all three diagnostic procedures on each patient.

For all three techniques the sensitivity, positive predictive value and accuracy for imaging Cockett I perforating veins were significantly lower than those for Cockett II and III veins. This is mainly a result of imaging problems due to the smaller diameter and length of Cockett I perforating veins and the fact that the perforator may be compressed by the tourniquet used in phlebography.

Pierik *et al.*[3] reported a sensitivity of 79 per cent for preoperative prediction of incompetent calf perforating veins by CDS, similar to the present results. However, there was a significant number of false-positive results in the current study so that a specificity of 100 per cent[3] could not be confirmed. The small group of patients examined by Pierik ($n = 20$) may explain the difference in specificity, although Müller *et al.*[4] also noted a significant number of false-positive veins in their study of 15 patients (20 legs).

Meyer *et al.*[5] found that CDS and ascending phlebography predicted the site of incompetent calf perforating veins with similar accuracy compared with the results of SEPS. The present study suggested that CDS is more sensitive than ascending phlebography. Considering the invasive nature of phlebographic studies and the risk of allergic reactions from contrast media, a combination of CDS and clinical examination should be considered the method of choice in preoperative screening for incompetent perforating veins of the calf. The use of ascending phlebography should be limited to patients for whom CDS is not available, or where its results are questionable.

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Outcome after septic complications in J pouch procedures

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Background: Despite the wide range of surgical approaches for pouch salvage, septic complications are among the main causes of pouch failure.

Methods: This study analysed the mode and outcome of various therapeutic approaches for pouch salvage and the impact of time of diagnosis, localization and form of septic complications on the risk of pouch failure in 131 patients with septic complications of a total of 706 patients undergoing a J pouch procedure.

Results: Septic complications consisted of 76·3 per cent fistulas, 15·3 per cent anastomotic breakdowns and 8·4 per cent pelvic abscesses. A total of 107 patients (81·7 per cent) with septic complications required a mean of 2·2 surgical procedures. The frequency of permanent defunctioning and excision of the pouch in the 131 patients with septic complications was 23·7 and 6·1 per cent respectively. The estimated cumulative 3-, 5- and 10-year rate of pouch failure in patients with septic complications was 19·6, 31·1 and 39·2 per cent respectively. The risk of pouch failure was significantly affected by the site of origin of septic complications ($P = 0.02$). The 5-year pouch failure rate increased in a subgroup of patients with septic complications at the pouch–anal anastomosis when the anal sphincter was involved (50·1 *versus* 29·2 per cent; $P = 0.18$).

Conclusion: Pouch failure as a result of septic complications may occur several years after ileal pouch–anal anastomosis. For prevention of pouch failure, surgery for septic complications is required in a high percentage of patients and repeated attempts are justified. Follow-up studies are required for further analysis of pouch failure.

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Introduction

Although the long-term functional results of ileal pouch–anal anastomosis (IPAA) are satisfactory[1,2], the outcome of this procedure may be compromised by a number of specific complications[3–6], among which septic complications have the most significant clinical implications. These include, in the worst case, a permanent defunctioning ileostomy or excision of the pouch[3,4,7–11]. Septic complications comprise anastomotic leaks, pelvic abscesses and pouch–anal fistulas. The prevalence of septic complications varies between 6 and 37 per cent[12–15].

Experience with the outcome of pouch salvage therapy may indicate whether repeated attempts to treat septic complications, including major surgical procedures, are justified or whether the occurrence of septic complications inevitably leads to pouch failure. By identifying the risk factors for pouch failure, surgical techniques can be refined and postoperative follow-up targeted optimally.

The aims of the present study were to analyse (1) the mode and outcome of therapeutic approaches for pouch salvage and (2) the impact of particular factors on the risk of pouch failure in patients with septic complications.

Patients and methods

Between January 1988 and June 1999, a total of 706 consecutive patients (494 patients with ulcerative colitis (UC) and 212 with familial adenomatous polyposis (FAP)) underwent IPAA. In a previous study, 131 patients were identified who developed septic complications, and risk factors for septic complications were analysed[15].

IPAA was introduced in this unit in January 1982. Experience with IPAA over the years up to January 1988 had shown that the localization of septic complications followed certain patterns. Based on this, a classification of septic complications was devised with respect to form and localization (*Fig. 1*, *Table 1*) and was used as the basis for this investigation.

The surgical procedure for IPAA consisted of abdominal proctocolectomy, complete transanal mucosectomy leaving a short rectal cuff with a length of 3–4 cm, construction of an ileal J pouch using two 90-mm linear staplers (GIA 90 Premium; United States Surgical, Norwalk, Connecticut, USA) and handsewn IPAA. No case of previously undetected Crohn's disease was identified by histological examination of the resected specimen.

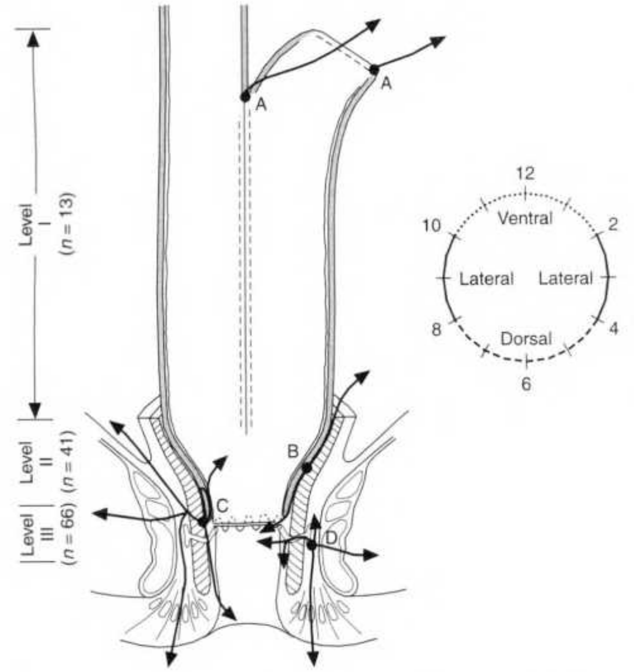

Fig. 1 Classification of septic complications, distinguishing between three levels within the pouch–anal region. A, blind-limb fistula; B, cuff fistula; C, fistula and separation of the ileal pouch–anal anastomosis; D, anal gland fistula. Anastomotic separation and fistulas in level II and III were assigned additionally to three sectors of equivalent perimeter, seen in the lithotomy position: ventral (10.00–2.00 o'clock), dorsal (4.00–8.00 o'clock) and lateral (2.00–4.00 and 8.00–10.00 o'clock)

Data from IPAA, follow-up consultations and treatment for septic complications were entered into a clinical registry and documented prospectively.

Diagnostic procedures for the detection of septic complications included digital and proctoscopic examination of the pouch–anal anastomosis and pouchoscopy at each follow-up visit. Diagnostic studies for the classification of septic complications comprised endosonography, magnetic resonance imaging, pouchography, computed tomography, and proctoscopy under general anaesthesia.

Septic complications were divided into parapouchal pelvic abscesses without fistulas and septic complications consisting of fistulas and anastomotic separation. Septic complications found at follow-up examination or during pouch salvage operations were documented by the clinician or surgeon respectively in an IPAA sketch designed for classification (*Fig. 1*). Three levels were distinguished within the pouch–anal region: level I comprised the upper and middle part of the pouch as well as a potential blind limb, level II represented the rectal cuff and level III represented the pouch–anal anastomosis. Anastomotic separation and fistulas in level II and III were additionally assigned to three sectors of equivalent perimeter, as seen in the lithotomy position: ventral (10.00–2.00 o'clock), dorsal (4.00–8.00 o'clock) and lateral (2.00–4.00 and 8.00–10.00 o'clock) (*Fig. 1*). In the ventral sector, pouch–vaginal fistulas were identified specifically and analysed separately.

Procedures for treatment of septic complications were classified into conservative therapy, including medical treatment and local irrigation, and minor and major surgical procedures. Minor surgical procedures were defined as limited transanal or perineal approaches whereas major

Table 1 Septic complications and their surgical therapy in 131 patients

Form and localization of septic complications		All patients	Operated patients	Surgical procedures			
				All	No. per patient*	Minor	Major
Parapouchal pelvic abscess		11	8	14	1·7(1·0)	7	7
Level I	Proximal pouch fistula	13	12	23	1·9(1·0)	4	19
Level II	Cuff fistula	41	36	84	2·3(1·4)	49	35
Level III	Anastomotic separation	20	12	29	2·4(1·7)	12	17
	Pouch–anal anastomotic fistula	31	25	54	2·2(1·1)	34	20
	Pouch–vaginal fistula	15	14	35	2·5(1·0)	8	27
Total		131	107	239	2·2(1·2)	114	125

*Values are mean(s.d.)

Table 2 Procedures for surgical treatment of septic complications in 107 patients

	No. of procedures (*n* = 239)
Minor surgery	
Transanal or perineal approach	114 (47·7)
Fistulotomy	50 (20·9)
Fistulotomy and mucosal advancement flap	14 (5·9)
Fistel excochleation/seton placement	21 (8·8)
Direct closure of the internal opening	11 (4·6)
Revision/closure of the anastomosis	11 (4·6)
Abscess drainage	7 (2·9)
Major surgery*	
Transabdominal approach	97 (40·6)
Abscess drainage	7 (2·9)
Ileostomy only	19 (7·9)
Fistula repair	32 (13·4)
Revision of pouch body/blind limb	13 (5·4)
Reconnection of the IPAA	22 (9·2)
Construction of a redo pouch	4 (1·7)
Extensive transanal or perineal approach	28 (11·7)
Cuff revision	5 (2·1)
Dorsal rectotomy	6 (2·5)
Muscle flap (gracilis or levator plastic)	10 (4·2)
Pouch advancement flap	6 (2·5)
Transvaginal revision	1 (0·4)

Values in parentheses are percentages. *Major surgical procedures involved ileal diversion in 104 (83·2 per cent) of 125 procedures. IPAA, ileal pouch–anal anastomosis

surgical procedures consisted of all transabdominal approaches and extensive transanal or perineal procedures (*Table 2*).

Pouch failure was defined as the need for pouch excision (absolute failure) or permanent dysfunction of the pouch with a covering ileostomy for more than 2 years (relative failure).

Statistical analysis

Statistical analysis was performed using SAS software (Release 8.10; SAS Institute, Cary, North Carolina, USA). The number of surgical procedures per patient was given as mean(s.d.). Because the follow-up after diagnosis of septic complications was heterogeneous, the distribution of pouch failure from the date of IPAA was estimated by the Kaplan–Meier method[16]. Patients without pouch failure at the latest follow-up were censored. Univariate and multivariate hazard ratio (HR) estimates and corresponding 95 per cent confidence intervals (c.i.) were computed by using Cox proportional hazards regression analysis[17]. $P < 0{\cdot}05$ was considered to be statistically significant. All tests were two sided.

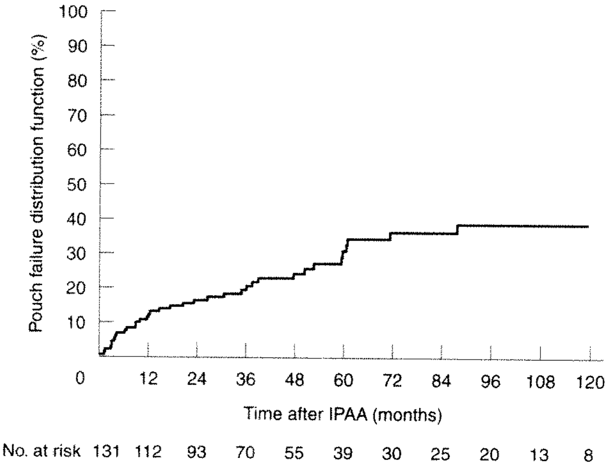

Fig. 2 Cumulative pouch failure rate in 131 patients with septic complications after ileal pouch–anal anastomosis (IPAA) calculated by Kaplan–Meier analysis

Results

Septic complications occurred in 131 (18·6 per cent) of 706 patients after IPAA. Some 76·3 per cent of all septic complications were fistulas; 15·3 per cent were anastomotic separations and 8·4 per cent were parapouchal abscesses. Furthermore, 9·9 per cent of septic complications occurred in level I, 31·3 per cent in level II and 50·4 per cent in level III. Septic complications in level I were observed exclusively in the area of a blind limb (*Table 1*).

The overall frequency of pouch failure in patients with septic complications was 29·8 per cent (39 of 131 patients) (23·7 per cent relative and 6·1 per cent absolute failure). The estimated cumulative 3-, 5- and 10-year rate of pouch failure in all patients with septic complications was 19·6, 31·1 and 39·2 per cent respectively (*Fig. 2*).

Median follow-up time of patients without pouch failure at last follow-up was 51·5 (interquartile range 31·5–96·4) months.

Salvage therapy for septic complications

For surgical treatment of septic complications, 239 procedures (114 minor and 125 major) were performed in 107 patients with a mean of 2·2 approaches per patient. Pouch–vaginal fistulas and anastomotic separations required the highest mean number of operations (mean 2·5 and 2·4 respectively) (*Table 1*).

Septic complications were treated with conservative therapy alone in 24 patients (18·3 per cent), resulting in a relative pouch failure rate of 8·3 per cent (two patients). Minor surgery was employed as the most extensive

Table 3 Frequency and outcome of surgical treatment in 107 patients of a total of 131 patients with septic complications

Frequency of surgical treatment	No. of patients	Mode of surgical treatment		Pouch failure (%)		
		Minor	Major	All	Relative*	Absolute†
1	36	19	17	19·4	19·4	0
2	39	39	39	35·9	30·8	5·1
3	22	33	33	40·9	27·3	13·6
> 3	10	23	36	70·0	40·0	30·0
All patients	107	114	125	34·6	27·1	7·5

Twenty-four patients who received exclusively medical treatment were excluded from this analysis. *Ileostomy for more than 2 years; †pouch excision

procedure in 33 patients (25·2 per cent), resulting in a relative pouch failure rate of 6·1 per cent. Septic complications were treated with major surgery as the most extensive procedure in 74 patients (56·5 per cent), resulting in a relative failure rate of 36·5 per cent and an absolute pouch failure rate of 10·8 per cent.

Of all patients with septic complications who underwent surgical therapy, 33·6 per cent were treated with only one procedure, with a 19·4 per cent rate of relative failure and no absolute pouch failure. The rates of both relative and absolute pouch failure increased with increasing numbers of surgical treatments (*Table 3*).

Pouch failure owing to septic complications occurred when treatment of septic complications was not successful (35·9 per cent persisting fistulas) and when long-standing inflammatory processes had resulted in secondary complications (17·9 per cent insufficiency of the anal sphincter, 12·8 per cent pouch outlet obstruction, 10·3 per cent pelvic fibrosis, 10·3 per cent pouchitis and 12·9 per cent patient refusal of closure of ileostomy).

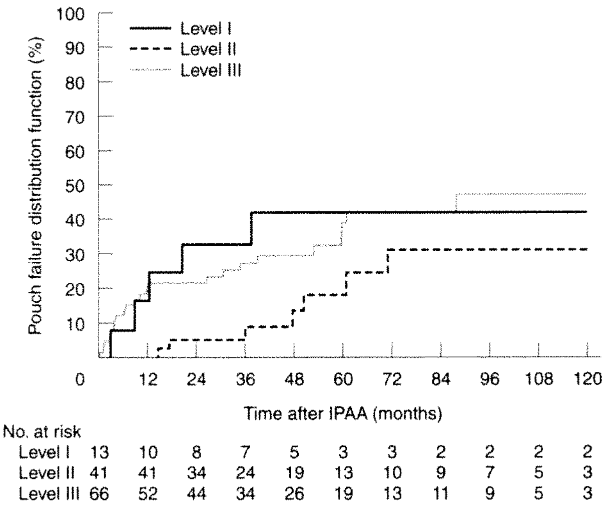

Fig. 3 Distribution function of pouch failure rate after ileal pouch–anal anastomosis (IPAA) in patients with septic complications at levels I, II and III (Kaplan–Meier estimation)

Risk factors for pouch failure in septic complications

The level of fistulas and anastomotic separation was identified as having a significant effect on the risk of pouch failure. Univariate analysis determined a significantly decreased estimated risk of pouch failure from level I (5-year rate 46·5 per cent) and level III (5-year rate 39·2 per cent) to level II (5-year rate 18·3 per cent) (HR 0·41 (95 per cent c.i. 0·18 to 0·95); $P = 0{\cdot}02$) (*Fig. 3*). The estimated risk of pouch failure increased when fistulas (5-year rate 34·3 per cent) or anastomotic separations (5-year rate 21·3 per cent) were diagnosed, compared with parapouchal abscesses (5-year rate 12·5 per cent), but this increase just failed to reach statistical significance (HR 0·30 (95 per cent c.i. 0·04 to 2·20); $P = 0{\cdot}15$).

The risk of pouch failure among patients with septic complications was affected only by the vertical location of the fistula or anastomotic breakdown in univariate analysis (*Table 4*). Multivariate analysis confirmed that the localization of fistulas and anastomotic separations was independently associated with the risk of pouch failure. The final model of multivariate analysis determined a significantly increased risk of pouch failure from parapouchal abscesses or from septic complications located at level II to septic complications located at level III and level I (HR 2·65 (95 per cent c.i. 1·21 to 5·82); $P < 0{\cdot}01$).

In a subgroup of 108 patients in whom 107 septic complications were located at levels II or III and one dorsal cuff fistula originated from the blind limb of the pouch, the rate of pouch failure was assessed with respect to location of fistulas and/or anastomotic separation in one of the three horizontal sectors (dorsal, lateral or ventral) and to pouch–vaginal fistulas. The estimated 5-year rate of pouch failure was 43·0 per cent for patients with pouch–vaginal fistulas, 26·1 per cent for patients with ventral fistulas and 38·4 per

Table 4 Results from univariate analyses of potential risk factors for pouch failure in 131 patients with septic complications

Factor	*n*	Events*	Hazard ratio†	*P*
Gender				0·49
Male	70	18 (25·7)	1	
Female	61	21 (34·4)	1·25 (0·66, 2·37)	
Age at IPAA (years)				0·96
< 32	64	21 (32·8)	1	
≥ 32	67	18 (26·9)	1·02 (0·53, 1·93)	
Underlying disease				0·78
Ulcerative colitis	112	34 (30·4)	0·87 (0·33, 2·26)	
Familial adenomatous polyposis	19	5 (26·3)	1	
Ileostomy at time of IPAA				0·77
Yes	113	36 (31·9)	1·19 (0·36, 3·93)	
No	18	3 (16·7)	1	
Colectomy before IPAA				0·25
Yes	39	16 (41·0)	1·49 (0·78, 2·87)	
No	92	23 (25·0)	1	
Form of septic complication‡				0·15
Parapouchal pelvic abscess	11	1 (9·1)	0·30 (0·04, 2·20)	
Anastomotic separation	20	4 (20·0)	1	
Fistula	100	34 (34·0)	1	
Time of diagnosis after IPAA (months)‡				0·64
< 6	69	14 (20·3)	1	
≥ 6	62	25 (40·3)	1·17 (0·60, 2·30)	
Vertical location of fistula and anastomotic separation				0·02
Level I	13	7 (53·9)	1	
Level II	41	7 (17·1)	0·41 (0·18, 0·95)	
Level III	66	24 (36·4)	1	
Horizontal location of fistula and anastomotic separation§				0·38
Dorsal	21	6 (28·6)	1	
Lateral	4	0 (0)	1	
Ventral	68	18 (26·5)	1	
Pouch–vaginal	15	8 (53·3)	1·47 (0·63, 3·45)	
Involvement of anal sphincter¶				0·18
Yes	23	12 (52·2)	1·74 (0·77, 3·96)	
No	43	12 (27·9)	1	
Total	131	39 (29·8)		

Values in parentheses are *percentages or †95 per cent confidence intervals. ‡Patients with more than one septic complication are included in the analyses with their main septic complication. §Analysed in a subgroup of 108 patients in whom 107 septic complications were located in levels II or III and one dorsal cuff fistula originated from the blind limb of the pouch; ¶analysed in a subgroup of 66 patients in whom septic complications were located in level III. IPAA, ileal pouch–anal anastomosis

cent for patients with dorsal fistulas. No pouch failure was caused by fistulas or anastomotic dehiscence occurring in the two lateral sectors. These differences were not statistically significant.

The estimated 5-year rate of pouch failure increased markedly when septic complications involved the anal sphincter. In a subgroup of 66 patients in whom septic complications were located at level III, the anal sphincter was involved in 34·8 per cent, resulting in an estimated 5-year pouch failure rate of 50·1 per cent compared with 29·2 per cent in patients with no involvement of the anal sphincter. However, this difference failed to reach statistical significance ($P = 0{\cdot}18$).

Discussion

The cumulative rate of pouch failure caused by septic complications in the present study was regarded as a time-dependent function and was therefore estimated by the Kaplan–Meier method, which was not performed in earlier investigations[3,18–22]. It becomes evident that septic complications result in pouch failure in a considerable number of cases and are therefore a serious threat to the long-term outcome of IPAA.

The pouch–anal anastomosis[9,20,23–25] and the rectal cuff[25] are recognized areas for the development of septic complications. This is confirmed by the present findings.

However, the risk of pouch failure due to septic complications in the region of the rectal cuff was relatively low, which counters reservations expressed against the handsewn technique with a short rectal cuff for construction of the pouch–anal anastomosis[26].

The findings presented here show that conservative therapy is not sufficient in most cases of septic complications. Only 16·8 per cent (22 patients) of septic complications could be managed successfully with conservative therapy alone, whereas surgical treatment was required in the vast majority.

The overall success rate of pouch salvage in patients with septic complications in this study compares favourably with other reports[8,9,20,21]. There has been controversy as to whether repeated surgical attempts at pouch salvage are justified[11,27,28]. The mean number of minor and major surgical procedures in all patients with septic complications registered in the present investigation was 2·2 per patient, similar to the findings of earlier studies, in which mean numbers of 2·0, 2·4 and 2·9[3,11,24] were reported. With a frequency of up to three remedial operations for the treatment of septic complications in the present patients, the success rate was still as high as 60 per cent. This corresponds to earlier observations of success rates of more than 50 per cent in attempts at pouch salvage by multiple procedures[27]. However, the prospect of success appears to decrease markedly as soon as the number of attempts at pouch salvage rises beyond a certain threshold of repeated procedures, or as soon as minor surgery is no longer sufficient to treat septic complications. This finding may be important for estimating the risk-to-benefit ratio of repeated or extended surgical procedures for pouch salvage.

It has been demonstrated previously that patients with FAP have a lower risk of septic complications than patients with UC[4,5,12,21,23,24]. The estimated cumulative risk for septic complications (Kaplan–Meier analysis) was significantly higher in patients with UC than in those with FAP (estimated 3-year septic complication rate 24·2 and 9·2 per cent respectively), as shown previously[15]. However, the present study demonstrated that once septic complications had occurred, no significant difference was found in the risk of pouch failure between patients with UC or FAP.

The risk of pouch failure was significantly higher when septic complications occurred in level I (middle and upper part of the pouch) or in level III (pouch–anal anastomosis) than in level II (rectal cuff). All septic complications in level I were fistulas located in the area of the blind limb. It is conceivable that bacterial stasis similar to that in stagnant loop syndrome[28–30] accounts for septic complications in this area, and the high risk of pouch failure may be explained by the fact that no anatomical structures confine the extension of the septic process into the pelvis. This might result in pelvic fibrosis and a non-compliant pouch. As a consequence of this result, an ileoanal pouch is not constructed with a blind limb[29].

The ventral part of the pouch–anal region showed a high propensity for the development of septic complications. This was indicated by a high frequency of septic complications in the ventral sector and by the large number of surgical procedures and rate of pouch failure in pouch–vaginal fistulas. High rates of pouch failure in patients with pouch–vaginal fistulas may be explained by the close anatomical relationship of the dorsal vaginal wall to the pouch–anal anastomosis and the rectal cuff. Previous investigations[24,31,32] have described in detail the difficulties and great demands placed on the surgeon's expertise in treating pouch–vaginal fistulas. However, there is little agreement upon possible origins of pouch–vaginal fistulas. Some believe that handsewn anastomoses predispose to pouch–vaginal fistulas[27] and others the stapled anastomosis[25]. It has also been speculated that a short rectal cuff might play a role in the development of pouch–vaginal fistulas[25].

Involvement of the anal sphincter by septic complications increased the risk of pouch failure in this study, reflecting the fact that the anal sphincter is of central importance for the function of the pouch. Dysfunction of the anal sphincter can be caused either by acute inflammatory or chronic fibrotic processes of septic complications.

Pouch failure represents a serious risk in patients who develop septic complications and may occur several years after IPAA. To prevent pouch failure, surgical therapy is required in a high percentage of patients with septic complications and repeated surgical attempts are justified.

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Original article

Evidence for separate disease phenotypes in intestinal Crohn's disease

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Background: This study investigated the hypothesis that separate phenotypes of Crohn's disease exist which display differing patterns of recurrence with a tendency to preservation of phenotype between serial operations.

Methods: Some 483 abdominal operations (278 patients) were identified from a prospectively compiled database. Patterns of recurrence (reoperation) were analysed by Kaplan–Meier plots and log rank tests according to disease phenotype (perforated, stenosed or ulcerated). Serial operations were analysed by agreement of phenotype and microscopic features of disease using kappa statistics and correlation coefficients.

Results: There was no significant difference in recurrence according to disease phenotype (median reoperation-free survival time 43·0, 50·2 and 47·9 months for perforated, stenosed and ulcerated types respectively; log rank $\chi^2 = 3{\cdot}5$, $P = 0{\cdot}18$). There was poor agreement in phenotype between serial operations ($\kappa = 0{\cdot}22$ for first/second operation and $\kappa = 0{\cdot}15$ for second/third operation) and no significant correlation between pathological features was identified (r between $-0{\cdot}19$ and $0{\cdot}48$).

Conclusion: No evidence was found for the existence of separate disease phenotypes with differing natural histories or underlying pathological characteristics.

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Introduction

Crohn's disease may present with a wide variety of clinicopathological 'scenarios' including fistulation, perforation, ulceration and stricture formation[1–5]. The suggestion that there may be separate 'phenotypes' of disease is not new. Previous studies from Mt Sinai Hospital[6] suggested that patients grouped according to 'perforating' or 'fibrostenosing' presentations had differing patterns of recurrence with a tendency to preservation of the presenting phenotype in subsequent recurrences. This was also the finding from Rome[7] and Japan[8]. Others investigators, however, have not found this to be the case[9]. Indeed, using a slightly different classification of patients' phenotypes, subsequent analysis of the Mt Sinai data has not confirmed the original findings[10].

Such a classification might be a useful tool for investigation of disease pathophysiology in the laboratory and in the clinical setting where certain drug therapies may be more effective at preventing recurrence in different disease 'phenotypes'[11]. It might allow a formal subgrouping of patients in trials for purposes of analysis. One problem is exactly how to define the phenotypes, particularly as several features of disease may be present in the same patient at any given recurrence. A previous prospective study of the relationship between 'phenotypes' assigned at surgery and the histological features present in the diseased bowel[12] showed small but significant differences between specimens classified as 'perforated', 'stenosed' or 'ulcerated'. Using this classification, a retrospective study of a database of patients with Crohn's disease was undertaken to investigate the patterns of phenotype present in serial resections and the correlation between serial resections and pathological features of disease.

Patients and methods

A database of surgery for Crohn's disease has been compiled and maintained since 1986. Data have been recorded contemporaneously by the use of patient record cards which, together with details recorded in the operation and pathology notes, are entered prospectively into a database following discharge. This database was used to investigate the patterns of disease presentation in patients undergoing surgery for primary or recurrent enteric Crohn's disease.

All patients undergoing surgery for Crohn's disease were identified from these records and the sex, date of birth, age at operation and number of operations was noted. For each operation the following information was recorded: date, disease site (ileal, ileocolic, colonic), operation type (resection, strictureplasty, both), disease type (perforated, stenosed, ulcerated), major local complications (e.g. leak, haemorrhage, reoperation, obstruction), major system complications (e.g. cardiac complications, chest sepsis, thromboembolism), minor complications (e.g. urinary tract infection, minor chest complications) and date of recurrence.

Several criteria were used to select the records studied:

1. Procedures for perianal disease alone or surgery for non-recurrent disease (e.g. stomal complications) were excluded.
2. Operations were included only if full data were available.
3. Cases were recorded as 'perforated', 'stenosed' or 'ulcerated' from the operating note according to the following algorithm. The disease was considered to be perforated if there was written or drawn mention of abscess (retroperitoneal, interenteric, intramesenteric, pelvic or other), fistula or perforation. If these features were absent but one or more fixed strictures was identified the disease was classified as stenosed. Provided that the operating note confirmed features of Crohn's disease, any other cases were considered to be ulcerated.
4. Recurrence was defined as the need for further definitive surgery for enteric Crohn's disease.

Analysis of recurrence

Recurrence was analysed for all operations according to Kaplan–Meier methodology[13].

Phenotypes in serial operations

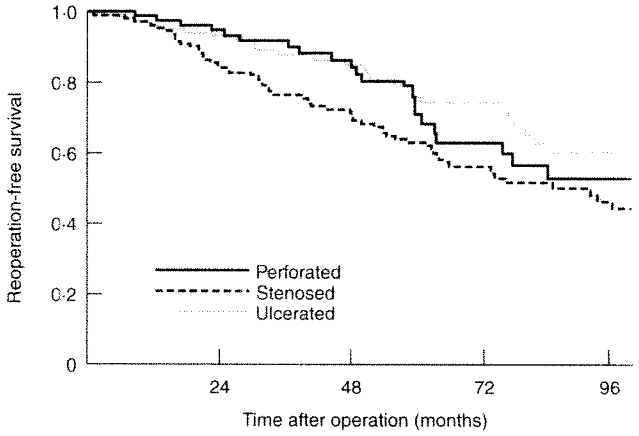
Patients who had two or more operations for recurrence were identified and each 'pair' of serial procedures was identified. The phenotypes of these operation pairs were investigated using kappa statistic analysis.

Pathological analysis

All patients who had two or more operations involving resection of affected bowel were identified. All available haematoxylin and eosin-stained slides taken from a full-thickness block of the specimen were retrieved from the cellular pathology department slide store. Microscopic analysis of the features of disease present was then conducted on a semiquantitative basis according to previously published methods[14]. The pathological features listed in *Table 1*, present in serial 'pairs' of resections, were then analysed by weighted correlation coefficients.

Table 1 Pathological features assessed in serial resection specimens[14]

Feature	Score
Corrected lymphoid aggregate score	0–4
Depth of lymphoid aggregate penetration	0–4
Corrected granuloma score	0–4
Perineural chronic inflammation score	0–3
Oedema score	0–3
Depth of neutrophil penetration	0–4



No. at risk	24	48	72	96
Perforated	82	68	43	22
Stenosed	173	126	88	51
Ulcerated	104	78	58	38

Fig. 1 Kaplan–Meier curves for reoperation-free survival according to phenotype. Median (range) reoperation-free intervals for perforated, stenosed and ulcerated types were 43·0 (0·3–145·9), 50·2 (0·2–305·3) and (47·9 (3·6–184·2) months respectively (log rank χ^2 = 3·5, 2 d.f., P = 0·18)

Completeness of dataset

Attempts were made to complete records using manual examination of the patient notes where information recorded in the database was incomplete. Analysis of the patient records suggested that less than 5 per cent of patients had been lost to follow-up to other hospitals.

Analysis of the data was performed by Kaplan–Meier plots and log rank test, kappa analysis and weighted correlation coefficients using the SPSS v10.0 package (SPSS, Chicago, Illinois, USA).

Results

Some 278 patients undergoing a total of 483 abdominal operations eligible for study were identified. Only one patient was excluded because of inability to determine the site of surgery at initial operation.

Fig. 1 shows the Kaplan–Meier survival curves for procedures according to operatively determined phenotypes. There was no significant difference in reoperation-free survival between the determined phenotypes according to log rank testing. Life-table analysis of recurrence risk by phenotype is presented in *Table 2*.

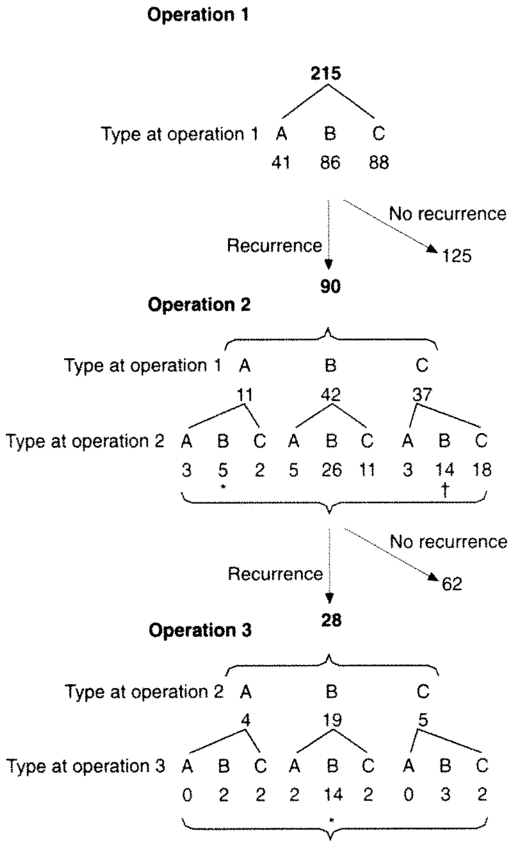
There was poor agreement in phenotype recorded between serial operations, either first and second or second and third (κ = 0·22 and κ = 0·15 respectively) (*Fig. 2*), although the data tend to suggest a higher degree of matching between serial operations for the 'stenosed' phenotype in both datasets.

There was no significant correlation identified between any of the pathological features studied in serial resections (*Table 3*) (*r* between –0·19 and 0·48).

Table 2 Life-table analysis of recurrence risk by phenotype

	Median survival (months)
Perforated	133·4 (81·8, 185·1)
Stenosed	132·4 (105·3, 159·6)
Ulcerated	155·2 (90·0, 220·4)

Values in parentheses are 95 per cent confidence intervals. Log rank $\chi^2 = 2{\cdot}20$, 2 d.f., $P = 0{\cdot}33$



	Type at operation 2			
	A	B	C	Total
Type at operation 1				
A	3	5	2	10
B	5	26	11	42
C	3	14	18	35
Total	11	45	31	87

κ = 0·22

	Type at operation 3			
	A	B	C	Total
Type at operation 2				
A	0	2	2	4
B	2	14	2	18
C	0	3	2	5
Total	2	19	6	27

κ = 0·15

Fig. 2 Relationship of phenotypes in serial operations. A, perforated; B, stenosed; C, ulcerated. Kappa agreement statistics are shown in table form. *One patient omitted; †two patients omitted

Table 3 Agreement between pathological variables studied in serial resection specimens

Feature studied*	Weighted kappa
Corrected granuloma score	−0·02
Corrected lymphoid aggregate score	0·06
Depth of lymphoid aggregate penetration	−0·19
Depth of neutrophil penetration	< 0·01
Submucosal oedema score	0·29
Perineural chronic inflammation score	0·46

*Scored 0–4

Discussion

The value of the concept of separate phenotypes of disease lies in its possible application as a tool in the investigation of disease pathogenesis as well as in the analysis of patients in clinical trials according to clinical phenotype. Differing pathophysiological mechanisms may exist in the pathogenesis of the phenotypes, allowing differing therapeutic approaches to be used.

The evidence for definable phenotypes is mixed[6,7,9,10,15]. One problem has been the method by which the phenotypes have been defined. Previous work has investigated the pathological features present in resected specimens classified prospectively according to a clear algorithm[14]; subtle differences in such phenotypes have been shown, supporting the use of such a classification to study the patterns of recurrence seen.

One difficulty with the present study is the application of a prospective classification algorithm to an historical archive. The algorithm relies heavily on the quality of the operation note to identify which features of disease were present and allow an accurate classification. Although there was no standard pro forma for the recording of operative findings during this period, it has been standard practice to record the presence of all fistulas, abscesses, stenoses and perforations identified peroperatively.

Another potential problem is the use of reoperation as an endpoint of recurrence. Undoubtedly this gives an overall apparent lower recurrence rate than clinical or radiological endpoints[16] but it is arguably a more reliable endpoint.

The analysis of reoperation-free survival by the Kaplan–Meier method suggests no difference between the proposed phenotypes according to recurrence risk. It has been suggested that a perforating form of the disease is associated with a more aggressive pattern of recurrence[6] and such differences would tend to support the presence of separate disease forms. Clearly there is no need for the different phenotypes to exhibit different 'recurrence behaviours' but the lack of difference is indirect evidence against the existence of separate phenotypes.

A central theme to the concept of disease phenotypes is that of phenotypic preservation within individual patients. The original data from Mt Sinai, Rome and Japan[6–8] suggested this. Indeed, subgroupings of patients might only be expected to be clinically or experimentally useful if the subgroupings were to run true according to phenotype in subsequent behaviour. In this study three phenotypes were defined since it is argued that some cases do not clearly fit into a simple binary (fibrostenosing/perforating) approach. Thus the overall poor relationship between serial recurrences is significant and in accordance with the Cleveland Clinic data[9].

Previous work has demonstrated the validity of using single sections to sample microscopic elements of disease and suggests that there are differences in the pathological features seen in specimens classified as described here[14]. It might be expected that if there were differences in disease behaviour these would be reflected in the pathological findings. There was very poor correlation in the scores for the features studied between serial resections in the same patient and the findings suggested that no real differences in the pathological features were present in the different phenotypes. Any differences may be explained by the specimens being from disease of different duration but all the specimens were from patients coming to definitive surgery and were thus likely to represent disease of a mature or 'endstage' nature.

Recurrence in Crohn's disease remains a major problem and is associated with high rates of reoperation whatever the indication for the first operation. From the present data there is no evidence to support the useful classification of Crohn's disease into different phenotypes according to operative findings, either on the basis of recurrent behaviour, preservation of phenotype or pathological features seen at serial reoperations.

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Short note

Cancer recurrence along the pouch longitudinal suture line after colonic J pouch–anal anastomosis

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Introduction

Local recurrence following proctectomy for cancer occurs in approximately 10 per cent of patients[1, 2] at the site of the anastomosis or on the pelvic side walls, with or without distant recurrence. Anastomotic suture-line recurrences are well recognized[1], but less well known are recurrences on suture lines other than at the anastomosis.

During follow-up of patients after rectal resection followed by colonic J pouch–anal anastomosis (CPAA), local recurrence situated on the pouch staple lines, separate from the circular coloanal anastomosis (*Fig. 1*), was observed in six patients.

Patients and methods

Between January 1988 and December 1997, 255 patients underwent CPAA for rectal cancer. All pouch–anal anastomoses were performed manually at the dentate line as described previously[3]. Surgery was preceded by mechanical bowel preparation and rectal washout with 5 per cent povidone–iodine. After clamping immediately below the tumour, the anal canal and low rectum were again irrigated with 5 per cent povidone–iodine. The colon above the cancer was not ligated before tumour mobilization.

Standard follow-up was performed with serial measurement of carcinoembryonic antigen level and abdominal ultrasonography every 6 months. Colonoscopy was performed at 1 year and every 3 years thereafter, or annually if polyps were identified.

Results

Thirty-two patients were found to have local recurrence, outside the pouch on the pelvic side walls in 23 patients and within the pouch in nine. Of these, three recurrences were at the level of the CPAA and six were on the longitudinal suture lines of the pouch, clearly distinct from the pouch–anal anastomosis. In nine patients there was associated metastatic disease.

Of the six patients with longitudinal staple-line recurrence, the original tumour was stage I in one patient, stage II in four and stage III in one. The mean distance of the tumour above the anal margin was 6·3 (range 4–8) cm and the mean resection margin was 2·9 (range 1–5) cm. One patient received neoadjuvant chemotherapy. Recurrence was detected a median of 15·5 (range 10–33) months after operation. Three patients were asymptomatic and three were symptomatic with rectal bleeding, iron deficiency anaemia and diarrhoea.

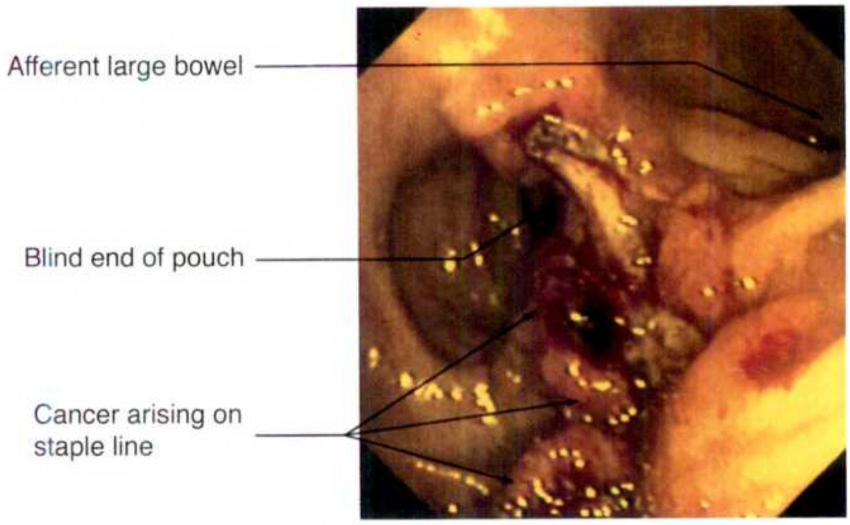

Fig. 1 Endoscopic view of recurrence arising on proximal pouch suture line

All patients underwent reoperation with curative intent. In four patients a sphincter-preserving procedure was performed (repeat CPAA in three patients and straight coloanal anastomosis in one) and two patients had an abdominoperineal resection. One patient with a liver metastasis underwent a hepatic wedge resection. One patient underwent a right hemihepatectomy and pulmonary wedge resection for metastatic disease 1 year after the primary operation and 2 years before developing recurrence within the pouch. In all cases the pathological appearance of the primary and recurrent tumour was comparable. Two patients had adjuvant chemoradiotherapy.

Five patients are alive and free of recurrence, and one is alive with recurrence, at a median follow-up of 40 (range 21–60) months.

Discussion

Suture-line recurrence after rectal resection may be due to several causes: implantation of free intraluminal cancer cells on raw surfaces or the suture material; instability of the mucosa at the site of an anastomosis; positive distal margin of resection; or instability of the mucosa in the vicinity of the primary tumour and therefore at the margin of resection. In the present patients the two latter mechanisms are unlikely, the pouch being constructed using colon distant from the primary rectal cancer. The pathological similarities between the primary and recurrent tumours are in keeping with implantation of cancer cells.

The presence of free cancer cells has been documented in the lumen of the colon proximal to the tumour independent of the tumour stage, and these cells have been shown to be viable[1]. They may implant at the suture line, within a fistula-*in-ano* tract, or in perianal skin tears.

Prevention of cell implantation may be achieved by intraluminal irrigation using various tumoricidal agents; chlorhexidine–cetrimide and povidone–iodine appear to be the most efficient[4]. Irrigation of the low rectum below a clamp or after stapling should prevent cell implantation from this section of the bowel[5]. However, the present observations suggest that it may also be beneficial to prevent cell implantation from the colon above the specimen. A simple procedure is to ligate the sigmoid at the beginning of the procedure and after rectal resection to irrigate the proximal segment of the colon used for the pouch construction with a tumoricidal solution. These are the methods currently employed by the authors.

Patients with a pouch suture-line recurrence seem to have a good prognosis. Five of the present six patients were disease-free at 21–60 months after reoperation. Early detection allows appropriate treatment. As the majority of these recurrences occur within the first 24 months after resection, early and systematic endoscopic surveillance of the pouch is recommended during the first 2 years after resection.

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Original article

Cytoreduction including total gastrectomy for pseudomyxoma peritonei

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Background: Cytoreductive surgery supplemented by perioperative intraperitoneal chemotherapy is a therapeutic option for selected patients with pseudomyxoma peritonei syndrome. In some patients, the stomach and/or its vascular supply are so covered by mucinous tumour that total gastrectomy is required for complete resection.

Methods: Forty-five patients underwent total gastrectomy with a temporary diverting jejunostomy as part of the surgical treatment of pseudomyxoma peritonei syndrome of appendiceal origin. Heated intraoperative intraperitoneal chemotherapy with mitomycin was used in all patients, and 36 had early postoperative intraperitoneal 5-fluorouracil. To date, 39 patients have had second-look surgery and stoma closure; 37 had additional perioperative intraperitoneal chemotherapy. A prospective database was maintained on all patients.

Results: The median age was 47 (range 33–66) years. Median interval from diagnosis of pseudomyxoma peritonei to definitive cytoreductive surgery was 23 (range 0–140) months. Six patients presented with intestinal obstruction. The need for gastrectomy was predicted before operation by abdominal computed tomography. Mean operative time was 13 (range 9–17) h. Mean intraoperative requirement for packed red blood cells was 3·0 units, and that for fresh frozen plasma was 9·9 units. Six peritonectomy procedures, including total gastrectomy, were required for complete cytoreduction. All except seven patients were maintained on parenteral nutrition before second-look surgery for jejunostomy closure. All but two patients have resumed oral nutrition with discontinuation of parenteral feeding. There was one postoperative death and one late death. Thirty-seven patients are alive and disease-free, 0–56 months after initiation of treatment.

Conclusion: Total gastrectomy with a temporary diverting jejunostomy may be used to facilitate complete cytoreduction in patients with advanced pseudomyxoma peritonei syndrome.

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Introduction

The progression of peritoneal surface malignancy displays a predictable pattern of disease distribution throughout the abdomen and pelvis[1]. In an aggressive malignancy such as intestinal-type colon cancer the peritoneal implants are distributed randomly on peritoneal surfaces near to the primary cancer. The surface of the primary tumour, greater omentum and paracolic gutters contain the majority of implants. In minimally invasive mucinous tumours coming from a perforated appendix, the predominant mass of peritoneal implants is redistributed by the flow of peritoneal fluid to dependent sites (pelvis and right retrohepatic space) and to sites of peritoneal fluid resorption (greater omentum and right hemidiaphragm)[2,3]. Mobile surfaces such as the small bowel and its mesentery may be completely free from tumour. This observation encouraged extensive parietal peritoneal and visceral resections with near-complete preservation of small bowel. In some patients with pseudomyxoma peritonei, complete cytoreduction requires peritonectomy, combined with total gastrectomy. To prevent the progression of microscopic residual disease the peritoneal space is treated intraoperatively and early after operation with intraperitoneal chemotherapy[4,5].

In the past, pseudomyxoma peritonei has been managed by serial debulking procedures. Gough and colleagues[6] reported a median disease-free survival of 18 months, and only a few patients remained disease-free at 5 years. Improved results of treatment have become apparent as complete cytoreduction was attempted and intraperitoneal chemotherapy was used[7–11]. Other groups have not accepted the profound impact of aggressive treatment on survival and suggest that outcomes depend on histopathological subgroups of the disease[12].

With a complete parietal peritonectomy a prolonged paralytic ileus is observed; the small bowel may fail to move bile and other enteric contents by peristalsis for 2–3 weeks. Prolonged enteric drainage of the small bowel is necessary to decompress the gut and thereby allow suture lines, especially an oesophagojejunal anastomosis, to heal safely. Nasojejunal tubes do not allow adequate drainage of enteric contents. In a previous study of eight patients who had gastrectomy, duodenostomy tubes were used but caused a high incidence of complications; the most common complication was enteric leakage around the duodenostomy tube insertion site[13]. Furthermore, if the duodenostomy tube failed to function properly the oesophagojejunal anastomosis disrupted.

In the past, five different peritonectomy procedures have been reported: anterolateral peritonectomy (greater omentectomy–splenectomy plus stripping of paracolic gutters), left subphrenic peritonectomy, right subphrenic peritonectomy, cholecystectomy–lesser omentectomy plus stripping of the omental bursa, and pelvic peritonectomy with rectosigmoid resection[14]. When total gastrectomy is added as a sixth peritonectomy the requirement for reliable prolonged enteric decompression is evident. In this clinical situation a temporary diverting jejunostomy has been used in 45 patients to protect the oesophagojejunal anastomosis. The diverting stoma was closed 3–6 months later at the time of second-look surgery. The purpose of this manuscript is to present an experience of total gastrectomy and diverting jejunostomy in patients with pseudomyxoma peritonei syndrome who required total gastrectomy for complete cytoreduction.

Patients and methods

Over a 14-year interval, 381 patients with pseudomyxoma peritonei syndrome from a perforated appendiceal tumour had a complete cytoreduction. This was defined as removal of all visible tumour down to nodules 2·5 mm or less in diameter. In October 1996 a new approach to cytoreductive surgery in patients with large-volume perigastric disease was formulated. Since this time all patients requiring complete cytoreduction have been managed using this approach. The clinical data on 45 patients who had total gastrectomy with a temporary diverting jejunostomy are the focus of this study.

Surgical technique

In this approach to complete cytoreduction, the stomach and the majority of the parietal and visceral peritoneum were resected. The majority of the small bowel was preserved. Heated intraoperative intraperitoneal chemotherapy with mitomycin C was given[5]. After intraoperative therapy, a circular stapled oesophagojejunal anastomosis was performed (ILS 29; Ethicon, Cincinnati, Ohio, USA). The duodenum, which was stapled off as part of the gastrectomy, was oversewn with interrupted sutures. The proximal jejunum was brought out through the left upper quadrant through a generous tunnel. The stoma was constructed as an end-jejunostomy. The Roux-en-Y anastomosis of the first portion of the jejunum to the proximal jejunal segment was not performed. All bile and pancreatic secretions exited via the diverting jejunostomy (*Fig. 1*). If the tumour was thought to show an aggressive character (mucinous carcinoma or hybrid mucinous tumour), 5 days of early postoperative intraperitoneal 5-fluorouracil (5-FU) was administered[5]. Thirty-six patients had perioperative 5-FU.

Patients were maintained on parenteral nutrition for 1–9 months until second-look laparotomy was performed. At this time, all adhesions were taken down, an additional cycle of heated intraoperative intraperitoneal chemotherapy was given and the jejunostomy was closed. If tumour nodules were present, they were cytoreduced before the chemotherapy. If the malignancy retained an aggressive character another 5 days of early postoperative intraperitoneal 5-FU was administered.

All of these patients were included in a prospective morbidity and mortality database. This database was specifically defined to itemize all postoperative events

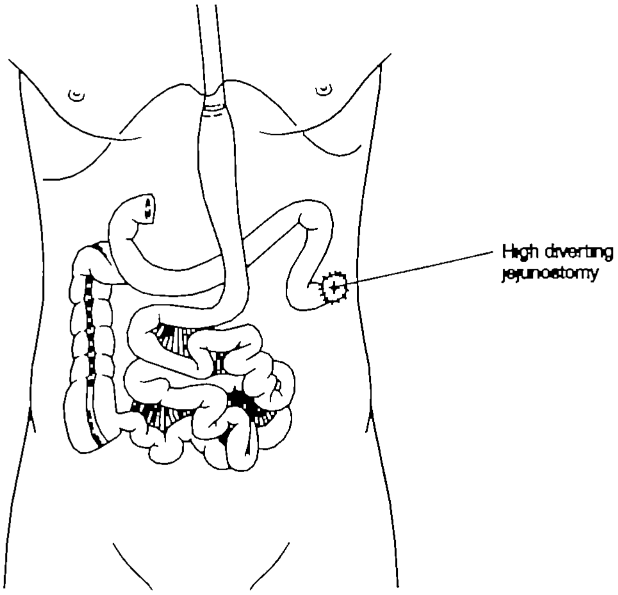

Fig. 1 Gastrectomy with temporary diverting jejunostomy as part of cytoreductive surgery for pseudomyxoma peritonei

while the patient was in hospital. Grade 3 complications were defined as those requiring an invasive intervention, usually an interventional radiology procedure. Grade 4 complications required a return to the operating room.

Results

The median age of the 45 patients was 47 (range 33–66) years. Pathology reported from the definitive cytoreduction was adenomucinosis in 19 patients, hybrid mucinous tumour in 21 and mucinous carcinoma in five. Fourteen patients had no, or only minor surgical procedures before the definitive cytoreduction, but eight had undergone two or three previous attempts at complete cytoreduction at other institutions. Six patients had intestinal obstruction and were maintained at least in part by intravenous feeding before surgery; two of these patients had had multiple previous attempts at cytoreduction at another hospital. In all patients computed tomography (CT) performed just before the cytoreduction showed extensive tumour within the subpyloric space[15]. This CT prediction of the need for gastrectomy facilitated a proper consent for surgery before the operation (*Fig. 2*). Forty of the patients had a Karnofsky nutrition score of 1; however, five patients whose disease had progressed to cause intestinal obstruction were showing increasing debilitation from pain and inadequate nutrition. The median interval from diagnosis of pseudomyxoma peritonei to definitive cytoreduction was 23 (range 0–140) months.

Surgical results

In all patients five visceral and parietal peritonectomy procedures were performed before the gastrectomy. In four patients cytoreduction was done without gastrectomy, but gastrectomy was needed at a second operative procedure. In all 45 patients the total gastrectomy was accompanied by a diverting jejunostomy. In 18 patients a total abdominal colectomy was performed along with the total gastrectomy; five also had proctectomy. When both gastrectomy and abdominal colectomy were required this resulted in the construction of both a permanent right-sided end-ileostomy and a temporary left-sided jejunostomy. In six patients the small bowel could be preserved to within a few centimetres of the ileocaecal valve, allowing an ileorectal anastomosis to be performed. The cytoreduction, heated intraoperative chemotherapy and reconstruction took a mean time of 13 (range 9–17) h. Mean blood requirement was 3·0 (range 0–10) units of packed red cells and that for fresh frozen plasma was 9·9 (range 0–16) units. Thirty-eight patients required parenteral nutrition between gastrectomy and jejunostomy closure, despite the use of oral replacement of pancreatic enzymes. The median interval between cytoreduction and the second-look operation with stoma closure was 5 (range 2–8) months.

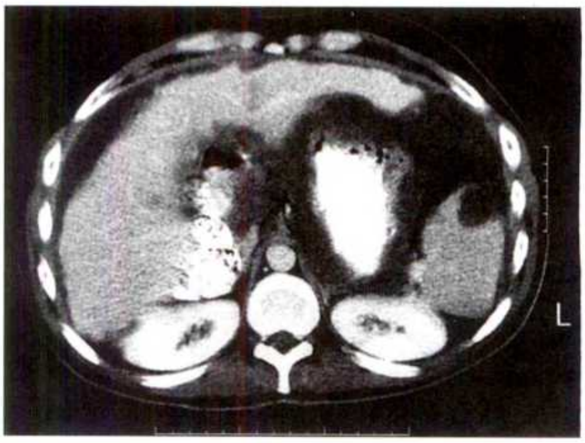

Fig. 2 Computed tomography of the upper abdomen in a patient with mucinous adenocarcinoma from a perforated appendix with advanced pseudomyxoma peritonei. The stomach is encased by mucinous tumour so that the left gastric artery is surrounded, and the tumour is impacted into the omental bursa

Outcome

There was a single postoperative death associated with pancreatitis and an oesophagojejunal anastomotic leak. A second death from other causes occurred 1-year after ostomy closure. A second oesophagojejunal anastomotic leak was associated with intractable postoperative vomiting. There were four reoperations for ileocolic or ileorectal anastomotic leakage, one reoperation for extensive fluid collection without fistula or sepsis, and two reoperations for bleeding. One small bowel fistula and one duodenal fistula were treated without reoperation. Three patients developed a pancreatic fistula. In 11 of the 45 patients there was a grade 3 or 4 complication. The median hospital stay was 37 (range 14–103) days.

Twenty-one of 39 patients who had a second-look laparotomy had visible evidence of persistent and progressive disease; in all but four, all tumour was cleared at the time of second-look surgery. As part of the comprehensive treatment strategy, all but two patients had a second cycle of heated intraoperative intraperitoneal chemotherapy with the combined second-look operation and stoma closure.

Forty-two of these 45 patients are alive and 37 are currently disease free. All patients who were disease free at the completion of second-look surgery have remained free from clinical evidence of recurrence. The median follow-up was 26 (range 0–56) months. All patients have CT of the chest, abdomen and pelvis every 6 months to monitor disease progression or recurrence.

Four significant complications (no deaths) occurred with the second-look operation. One patient developed a fistula at the lower aspect of the closure of the proximal jejunum, probably as a result of improper nasojejunal tube placement. A second patient developed a duodenal fistula after extensive repeat cytoreduction. A third patient developed a bladder fistula and an ileorectal anastomotic leak. A fourth patient developed an abdominal wall fasciitis that required wide debridement and skin grafting. In all four of these patients extensive disease progression was observed at the time of second-look surgery and repeat cytoreduction was attempted.

The high diverting jejunostomy produced a daily mean loss of 650 ml of bile and pancreatic juice, and caused a severe malabsorption despite pancreatic enzyme replacement. These potential problems in management caused little or no difficulty if patients remained on parenteral feeding while the high diverting jejunostomy was functional.

Three-quarters of the patients no longer required parenteral feeding soon after the stoma closure/second-look procedure. All but two patients were free from intravenous feeding within 4 months of the jejunostomy closure. Refeeding of bile was not used in any patient. Intestinal motility continued as normal despite the high diversion so that patients were able to consume a postgastrectomy diet. No adverse events from bacterial overgrowth or intestinal dysmotility occurred.

Discussion

Previous publications on pseudomyxoma peritonei syndrome demonstrated that completeness of cytoreduction was the dominant prognostic feature in this group of patients. The extent of disease before surgery was not important in predicting outcome. Histological grade was significant, but complete clearing of the mucinous tumour was the dominant variable[3]. The clarity of these data regarding the absolute requirement for completeness of cytoreduction and the predictable disease progression if residual disease was left on the stomach provided the rationale to extend the visceral peritonectomy to include the entire stomach[16]. This has improved the ability to achieve a complete cytoreduction in a larger proportion of patients.

The cost–benefit analysis of this treatment plan could be questioned. However, the median age in this group of patients was 47 years. They have many years ahead if they can be cured. From a healthcare perspective it is less expensive to treat these patients definitively and send them back to a productive status in society than to perform repeated debulkings. This argument was developed in a comprehensive review article on the pseudomyxoma peritonei syndrome[3]. Nineteen of these 45 patients had a minimally aggressive mucinous appendiceal malignancy resulting in an indolent disease process; additional patients with disease progression may be seen. Five patients known to have persistent disease are currently alive with minimal symptoms. Although pseudomyxoma peritonei is a lethal disease it can be indolent, and survival over several years with a slowly progressive disease does occur.

The magnitude of the commitment these treatments require for the physician, patient and patient's family must not be overlooked. Not only did these patients undergo gastrectomy, but 18 also required a total colectomy to clear all visible evidence of the appendiceal mucinous tumour. They were maintained on parenteral feeding both in hospital and at home during the interval between cytoreduction and stoma closure. A second major operation was required for closure of the diverting jejunostomy and a second look. In nearly all patients one or more family members were present and living in the hospital room with the patients during their in-hospital care. The protracted hospitalization and complex postoperative care required a cancer centre with a commitment to the total care of patients with this rare disease.

In a majority of these patients a complete parietal peritonectomy was required to clear the mucinous tumour. This extensive surgery resulted in a prolonged paralytic ileus and a need for efficient removal of enteric secretions. In the author's experience nasojejunal tubes stenting the oesophagojejunal anastomosis are inadequate for this decompression. The temporary duodenal diversion has provided reliable control of enteric secretions and made cytoreduction with gastrectomy a treatment option for patients with advanced pseudomyxoma peritonei syndrome.

All patients will require a second operation for closure of the high diverting jejunostomy. This allows a second-look procedure for cytoreduction of small amounts of residual mucinous tumour and a second cycle of heated intraoperative and early postoperative intraperitoneal chemotherapy. Second-look surgery may be an essential part of a successful treatment strategy. In a majority of patients a small amount of persistent and progressive mucinous tumour was discovered and treated, despite a completely normal CT scan of the chest, abdomen and pelvis[17]. However, four patients had large-volume recurrence of mucinous tumour observed at the time of second look. All four of these patients developed major complications as a result of this renewed aggressive approach to treatment failure with the initial cytoreduction. Repeat cytoreduction of a large volume of disease may not be appropriate from this experience.

Surprisingly few adhesions were encountered at the second-look stoma closure. The thorough intraoperative washing with mitomycin C, immediate postoperative lavage with peritoneal dialysis solution and 5 days of 5-FU lavage resulted in minimal adhesions. Pelvic adhesions remained a problem and required extensive lysis; occasionally adhesions in the extreme left upper quadrant were also problematic. The right subphrenic space and right subhepatic space were not re-explored because of dense adhesions between the surface of the liver stripped of its capsule and the undersurface of the right hemidiaphragm stripped of its peritoneum. Also, the area in and around the oesophagojejunal anastomosis was deliberately avoided.

Second-look surgery is beneficial if the repeat resection is complete[18]. However, if additional cytoreductions of mucinous appendiceal tumour are necessary, the beneficial effects are rapidly lost. Requirement for third, fourth and fifth cytoreductions indicates a more aggressive disease process that cannot be eradicated by combined cytoreductive surgery and perioperative intraperitoneal chemotherapy (F. Mohamed and P. H. Sugarbaker, unpublished data).

After the immediate postoperative recovery, two problems remain with this new approach of extensive peritonectomy with total gastrectomy. First, the left upper quadrant stoma remains for approximately 6 months. Proximity of the stoma to the left costal margin, lack of a mound of skin, and a small width of flat skin surface at the edges of the stoma caused initial difficulties in maintaining a watertight appliance. Also, the stoma output is liquid and rich in enzymes, so that even small leaks are troublesome. Some patients requested stoma closure within 6 months because of difficulties with management.

Second, patients must be kept on parenteral nutrition in order to maintain a high level of physical activity before second-look surgery. Although oral food intake was normal, resorption without bile and normal pancreatic enzymes was poor. All but two patients had parenteral feeding discontinued after jejunostomy closure.

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Original article

Significance of immunohistochemical nodal micrometastasis as a prognostic indicator in potentially curable oesophageal carcinoma

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Background: The number of positive lymph nodes is an important prognostic predictor in patients with oesophageal cancer. However, the significance of nodal micrometastasis in patients with overt nodal metastasis is unknown. The aim of this study was to clarify the clinical implications of nodal micrometastasis in patients undergoing curative oesophagectomy for oesophageal cancer.

Methods: Cervical, mediastinal and abdominal lymph nodes systematically removed from 104 patients with oesophageal cancer were examined immunohistochemically to detect cells that stained positively for cytokeratins with the monoclonal antibody cocktail AE1/AE3. The postoperative course and survival rates were compared among patients with and without micrometastases, after numerical classification of overt metastatic nodes (none, between one and four, five or more).

Results: Univariate analysis showed T stage, nodal micrometastasis and number of overt nodal metastases to be significant prognostic factors after oesophagectomy. Multivariate analysis revealed nodal micrometastasis and number of overt nodal metastases to be independent prognostic factors. The presence of micrometastases had a significant adverse effect on postoperative survival in patients with no overt metastasis and in patients with one to four overt metastatic nodes, but no such impact in patients with five or more overt metastatic nodes.

Conclusion: Assessment of nodal status by both histological examination for overt metastases and immunohistochemical examination for micrometastases is useful in stratifying patients undergoing curative oesophagectomy.

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Introduction

Lymph node status assessed by conventional histological examination is the most important prognostic factor in patients undergoing oesophagectomy for oesophageal carcinoma[1]. The presence of lymph node metastasis has a strong adverse impact on patient survival even after extended radical oesophagectomy[2,3]. Some recent studies have reported that the number of positive nodes, i.e. the numerical grade of lymph node metastasis, can predict patient outcome more accurately after oesophagectomy than the spatial location of the metastatic nodes[4,5]. Previously, the authors showed that cure is likely only in patients with four or fewer metastatic nodes (5-year survival rate 71 per cent for patients with negative nodes and 36 per cent for those with one to four positive nodes), whereas no patient with five or more positive nodes survived more than 5 years after oesophageal resection. Therefore, patients with oesophageal carcinoma and four or fewer positive nodes are potentially curable[6].

Despite these findings, tumour recurrence is not rare after oesophagectomy, even when histological examination shows no lymph node metastasis. Recently, immunohistochemically demonstrated micrometastasis to the lymph nodes has been shown to have a significant adverse influence on survival in patients with oesophageal cancer and histologically negative nodes[7–9]. However, the incidence and clinical implications of nodal micrometastasis remain unclear in patients with oesophageal cancer and overt nodal metastasis.

The present study sought to determine the incidence and clarify the clinical significance of immunohistochemically demonstrated nodal micrometastases and to correlate these data with the stage of oesophageal cancer. The authors selected patients undergoing radical oesophagectomy combined with extensive lymphadenectomy to minimize the possibility of false-negative assessments for both occult and overt metastases to the lymph nodes. Patients were followed for at least 5 years after oesophagectomy to reliably evaluate the influence of the presence of nodal micrometastases on prognosis.

Patients and methods

Patients

Between 1985 and 1994, a total of 194 patients with invasive thoracic oesophageal cancer underwent radical oesophagectomy combined with cervical, mediastinal and abdominal lymphadenectomy. During this period, extensive lymphadenectomy was performed routinely as part of radical oesophagectomy for patients with invasive oesophageal cancer and with good performance status. Of these patients, 90 were excluded from the study because of incomplete tumour resection ($n = 18$), a synchronous extraoesophageal second primary cancer ($n = 20$), preoperative chemotherapy or radiotherapy ($n = 4$), tumour histology other than squamous cell carcinoma ($n = 12$), or follow-up for less than 5 years or death from unrelated causes ($n = 36$). The remaining 104 patients all had curative resection, defined as an R_0 resection by the Union Internacional Contra la Cancrum (UICC) tumour node metastasis (TNM) residual tumour classification[10]. After operation, 41 patients received adjuvant chemotherapy consisting of cisplatin, vindesine, 5-fluorouracil or tegafur, either alone or in combination; ten patients received both adjuvant chemotherapy and radiotherapy, and nine received adjuvant radiotherapy alone. The ages of the 104 patients ranged from 40 to 78 (median 61·3) years; there were 93 men and 11 women.

Primary tumour resection

Based on the UICC TNM classification[10], the 104 oesophageal carcinomas were classified into 28 T_1 tumours, 13 T_2 tumours and 63 T_3 tumours. Of the 28 T_1 tumours, two were intramucosal invasive carcinomas and the others were submucosal carcinomas. Among the 104 patients, six had a tumour in the upper thoracic oesophagus, 57 had a tumour in the mid-thoracic oesophagus and 41 had a tumour in the lower thoracic oesophagus. Histologically, all tumours were squamous cell carcinomas; 34 were well differentiated, 55 were moderately differentiated and 15 were poorly differentiated.

Lymph node resection

The technique of radical oesophagectomy with extensive lymphadenectomy has been reported in detail elsewhere[6]. Lymph nodes resected were defined using the nomenclature of the Japanese Society for Oesophageal Diseases[11]. Based on routine histological examination, 38 patients had no overt nodal metastasis and the remaining 66 had positive nodes. Of the 66 patients with positive nodes, 46 had four or fewer metastatic nodes and the other 20 had five or more positive nodes.

A total of 8053 lymph nodes were dissected from the 104 patients. Of these lymph nodes, 7769 had no evidence of metastatic disease by routine histological examination. All of the 7769 lymph nodes were included in the present study. The mean number of lymph nodes dissected per patient was 77·5 (range 36–170).

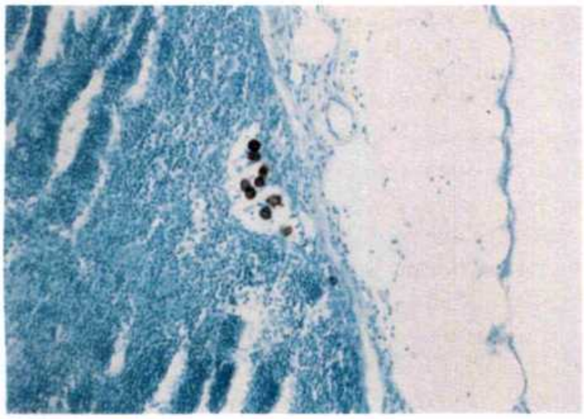
Based on a previous study which demonstrated that nine serial sections 3 μm thick (total thickness 27 μm) were sufficient to detect micrometastatic foci from colorectal cancer in lymph nodes[12], the authors examined five sections 10μm thick from each paraffin block of lymph nodes in the present study. The first and fifth sections were stained with haematoxylin and eosin for histological confirmation of the absence of overt metastatic tumour. The other three serial sections (30 μm in aggregate thickness) were used for immunohistochemical examination as described below.

Immunohistochemistry

The anticytokeratin antibody cocktail AE1/AE3 (Dako, Kyoto, Japan) was used at a dilution of 1 : 150. This mouse monoclonal antibody preparation is specific for human cytokeratins, and recognizes cytokeratins in epithelial cells[13]. The streptavidin–biotin immunoperoxidase method was used. Immunohistochemical staining was performed as described previously[7].

Definition of micrometastasis

Micrometastasis was defined as the presence of either a single cell (*Fig. 1a*) or a cluster of five cells or fewer (*Fig. 1b*) that was immunohistochemically positive for cytokeratin in a lymph node containing no overt metastatic deposits. Although reticular cells and plasma cells can show staining for cytokeratin, these non-neoplastic cells were discriminated from micrometastatic tumour cells by differing staining patterns as shown previously[12].


a Single cells

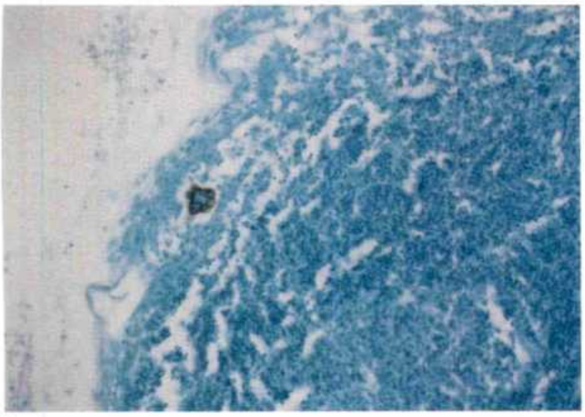

b Cluster of cells

Fig. 1 **a** Single tumour cells showing immunostaining for cytokeratin by an AE1/AE3 antibody cocktail (original magnification × 50). **b** Cluster of micrometastatic tumour cells detected by immunostaining with an AE1/AE3 antibody cocktail (original magnification × 50); reproduced with permission[7]

Follow-up data

Postoperative survival information was available in all 104 patients. Tumour recurrence developed in 53 patients, of whom 49 died from recurrent oesophageal cancer. Local or regional recurrence occurred in 24 patients, and recurrent disease developed at distant sites in 29 patients. Fifty-one patients survived more than 5 years with no evidence of recurrence.

Statistical analysis

Overall survival rates after resection were examined using the Kaplan–Meier method. The equality of survival curves was assessed using the log rank test. To elucidate factors influencing survival, ten factors, including patient characteristics, tumour status and postoperative treatment, were examined in all patients: gender, age (more than 61 *versus* 61 years or less), primary site (upper or middle *versus* lower oesophagus), grade of differentiation (poorly differentiated *versus* well or moderately differentiated), T stage (T_2 or T_3 *versus* T_1), lymphatic invasion, vascular invasion, nodal micrometastasis, overt nodal metastasis and adjuvant therapy. Cox's proportional hazard model[14] was used to identify whether these factors were independently associated with postoperative disease-free and overall survival. All analyses were performed using the SPSS 9.0 software package (SPSS Japan, Tokyo, Japan). $P < 0.05$ was considered significant.

Results

Incidence of nodal micrometastasis

Micrometastatic tumour cells were immunohistochemically visible as single cells (*Fig. 1a*) or small clusters of cells (*Fig. 1b*), with cytoplasmic staining by the anticytokeratin antibody cocktail AE1/AE3. All primary tumours resected from the 104 patients also showed diffuse staining with AE1/AE3.

Micrometastatic cells were found in 106 (1·4 per cent) of the 7769 overtly negative lymph nodes, and were present in 47 (45·2 per cent) of the 104 patients. According to the number of overt nodal metastases, nodal micrometastasis was found in 14 of 38 patients without overt nodal metastasis, 22 of 46 patients with one to four overtly positive nodes, and 11 of the 20 patients with five or more positive nodes. The number of lymph nodes containing micrometastases of tumour cells ranged from one to nine (median two) per patient.

Factors influencing postoperative disease-free and overall survival

Univariate analysis revealed that T stage ($P < 0.01$), nodal micrometastasis ($P < 0.01$) and number of overt nodal metastases ($P < 0.01$) were significant prognostic factors for both disease-free survival and overall survival (*Table 1*).

In the multivariate analysis, a backward stepwise selection for variable selection, with entry and removal limits of $P < 0.10$ and $P > 0.15$ respectively, was performed for all variables. Cox regression analysis showed that nodal micrometastasis and number of overt nodal metastases were the independent predictive factors for both disease-free and overall survival (*Table 2*).

Table 1 Results of univariate analysis for disease-free survival and overall survival

		P	
		Disease-free survival	Overall survival
Gender	Female	0·84	0·72
	Male		
Age (years)	≤ 61	0·06	0·12
	> 61		
Primary site	Lower	0·29	0·31
	Upper, middle		
Grade of differentiation	Well, moderately	0·96	0·81
	Poorly		
T stage	T_1	< 0·01	< 0·01
	T_2,T_3		
Lymphatic invasion	Absent	0·09	0·05
	Present		
Vascular invasion	Absent	0·27	0·69
	Present		
Micrometastasis	Absent	< 0·01	< 0·01
	Present		
No. of overt metastases	0	< 0·01	< 0·01
	1–4		
	≥ 5		
Adjuvant therapy	Performed	0·33	0·70
	Not performed		

Influence of micrometastasis on survival

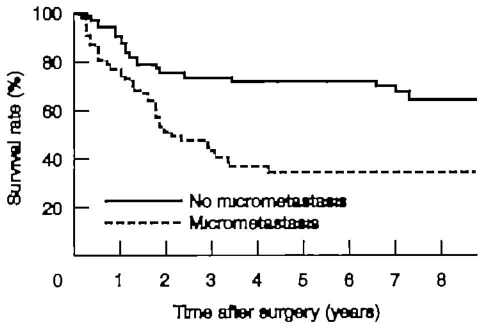
The overall survival curve of the 47 patients with nodal micrometastasis was significantly steeper than that of the 57 patients without nodal micrometastasis (*P* < 0·01) (*Fig. 2*). The 5-year survival rate for the former group was 34 per cent, whereas that for the latter group was 72 per cent.

Among patients without overt nodal metastasis, i.e. histologically negative nodes, the overall survival of the 14 patients with nodal micrometastasis was significantly worse than that of the 24 patients without micrometastasis (*P* < 0·05) (5-year survival rate 64 *versus* 92 per cent) (*Fig. 3*). Similarly, among patients with one to four overtly positive nodes, the overall survival of patients with nodal micromètastasis (*n* = 22) was significantly worse than that of patients without nodal micrometastasis (*n* = 24) (*P* < 0·01) (5-year survival rate 23 *versus* 71 per cent) (*Fig. 4*). However, the presence (*n* = 11) or absence (*n* = 9) of nodal micrometastasis had no significant impact on patient survival among patients with five or more positive nodes (*P* = 0·70) (5-year survival rate 18 *versus* 22 per cent) (*Fig. 5*). Moreover, there was no significant difference between the survival curve of patients with no overt metastases who had micrometastasis and the curve of patients with one to four overt metastatic nodes but no micrometastasis (*P* = 0·92). Similarly, the survival curve of patients with one to four overt metastatic nodes and

Table 2 Results of Cox regression analysis for disease-free survival and overall survival

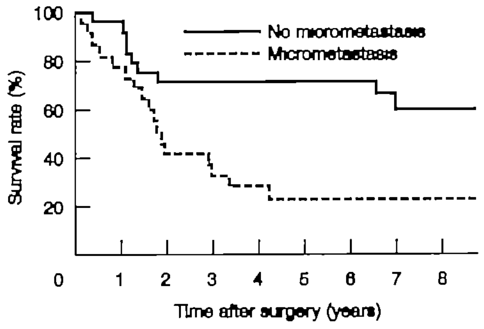
		Disease-free survival		Overall survival	
		RR	*P*	RR	*P*
Gender	Female	1·00		1·00	
	Male	1·25 (0·51, 3·07)	0·63	1·15 (0·47, 2·82)	0·76
Age (years)	≤ 61	1·00		1·00	
	> 61	1·51 (0·84, 2·74)	0·16	1·27 (0·69, 2·35)	0·44
Primary site	Lower	1·00		1·00	
	Upper, middle	1·20 (0·66, 2·16)	0·55	1·17 (0·63, 2·16)	0·62
Grade of differentiation	Well, moderately	1·00		1·00	
	Poorly	1·11 (0·49, 2·53)	0·81	1·13 (0·49, 2·58)	0·06
T stage	T_1	1·00		1·00	
	T_2,T_3	1·70 (0·66, 4·41)	0·27	1·72 (0·64, 4·59)	0·28
Lymphatic invasion	Absent	1·00		1·00	
	Present	1·38 (0·71, 2·68)	0·35	1·23 (0·60, 2·50)	0·57
Vascular invasion	Absent	1·00		1·00	
	Present	0·94 (0·53, 1·69)	0·84	1·20 (0·65, 2·20)	0·56
Micrometastasis	Absent	1·00		1·00	
	Present	2·85 (1·54, 5·27)	< 0·01	2·33 (1·23, 4·40)	< 0·01
No. of overt metastases	0	1·00	< 0·01	1·00	< 0·01
	1–4	3·11 (1·37, 7·08)		4·32 (1·77, 10·52)	
	≥ 5	5·58 (2·28, 13·63)		7·42 (2·84, 19·42)	
Adjuvant therapy	Performed	1·00		1·00	
	Not performed	0·74 (0·53, 1·69)	0·37	0·71 (0·36, 1·39)	0·31

Values in parentheses are 95 per cent confidence intervals. RR, relative risk



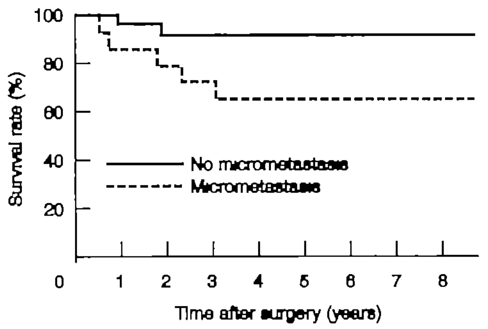
No at risk									
No micrometastasis	57	51	43	42	41	41	41	39	38
Micrometastasis	47	36	24	20	18	17	17	17	17

Fig. 2 Overall survival curves for patients with and without micrometastasis. $P < 0{\cdot}01$ (log rank test)



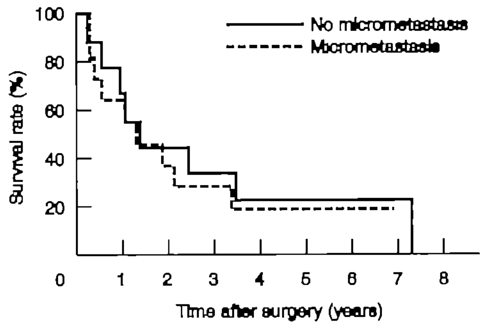
No at risk									
No micrometastasis	24	23	23	23	23	23	23	21	21
Micrometastasis	22	18	10	8	7	6	6	6	6

Fig. 4 Overall survival curves for patients with one to four overt metastatic nodes according to the presence or absence of micrometastasis. $P < 0{\cdot}01$ (log rank test)



No at risk									
No micrometastasis	24	23	22	22	22	22	22	22	22
Micrometastasis	14	12	11	10	9	9	9	9	9

Fig. 3 Overall survival curves for patients without overt metastasis according to the presence or absence of micrometastasis. $P < 0{\cdot}05$ (log rank test); reproduced with permission[7]



No at risk									
No micrometastasis	9	6	4	3	2	2	2	2	0
Micrometastasis	11	7	4	3	2	2	2	2	2

Fig. 5 Overall survival curves for patients with five or more overt metastatic nodes according to the presence or absence of micrometastasis. There was no significant difference between the two survival curves

concomitant micrometastasis was not significantly different from that of the patients with five or more overt metastatic nodes ($P = 0{\cdot}59$).

Postoperative relapse patterns

Seven of 14 patients with nodal micrometastasis from pathological stage N_0 (pN_0) oesophageal cancer had disease relapse: three patients had lymphatic and four patients had haematogenous recurrence (liver, bone, lung and muscle). In contrast, only two of 24 patients without nodal micrometastasis from pN_0 oesophageal cancer had a relapse after operation, both with haematogenous recurrence (lung and liver).

In patients with one to four positive nodes, 18 of 22 patients with nodal micrometastases had tumour recurrence (ten lymphatic, six haematogenous, one pleural and one anastomotic recurrence). Eight of 24 patients without nodal micrometastases had postoperative recurrent disease (five lymphatic, two haematogenous and one pleural recurrent tumour).

In patients with five or more positive nodes, ten of 11 patients with nodal micrometastasis had recurrence (three lymphatic, six haematogenous and one pleural dissemination). Eight of nine patients without nodal micrometastases had a relapse (four lymphatic and four haematogenous disease, involving lung, skin and bone).

Discussion

Several recent studies have demonstrated the frequent presence of micrometastatic tumour cells in the lymph nodes and bone marrow using epithelial-specific monoclonal antibodies or reverse transcriptase–polymerase chain reaction in many types of malignant tumours[15,16]. However, whether such micrometastases have clinical significance is controversial. Some authors have reported a lack of significant impact of micrometastasis on prognosis[17,18], while others have described adverse effects on patient outcome[19,20]. Glickman *et al.*[21] did not find a correlation between the presence of occult lymph node metastasis and poor survival for patients with oesophageal cancer. In contrast, Izbicki *et al.*[8] and Natsugoe *et al.*[9] have found nodal micrometastases to be a significant indicator of a poorer prognosis after oesophagectomy. The authors' previous study was consistent with the findings of the latter authors[7]. However, little is known about the clinical implications of micrometastases in patients with overt nodal metastasis from oesophageal cancer.

Oesophageal carcinomas are known to metastasize frequently to lymph nodes at a considerable distance from their primary sites, even at an early stage of local tumour extension[22]. Such tumour behaviour necessitates extensive lymphadenectomy to assess accurately the possibility of lymph node micrometastases. In the present study, all patients received extensive lymphadenectomy of the cervical, mediastinal and abdominal lymph nodes, which were mapped during or immediately after operation according to standardized anatomic criteria.

The number of overt metastatic nodes has been reported to strongly influence postoperative survival after curative oesophagectomy for oesophageal cancer[4,5]. In a previous study, cure was likely only in patients who had four or fewer positive nodes (5-year survival rate was 71 per cent for patients with negative nodes and 36 per cent for those with one to four positive nodes), whereas the prognosis was extremely poor in patients with five or more positive nodes, even after extended radical oesophagectomy combined with three-field lymphadenectomy[6]. These data suggest that patients with four or fewer overt positive nodes have potentially curable oesophageal cancer.

In the current study, the clinical significance of nodal micrometastasis as an independent prognostic indicator was confirmed in patients undergoing oesophagectomy for oesophageal cancer. Furthermore, nodal micrometastasis was also a significant prognostic factor in patients with potentially curable oesophageal cancer as defined by the numerical classification of positive nodes. Survival among patients with micrometastases was significantly worse than that of patients without micrometastases, not only in patients without overt metastasis (*Fig. 3*) but also in patients with one to four overtly positive nodes (*Fig. 4*). However, nodal micrometastasis had no impact on survival of patients with five or more overt metastatic nodes; the prognosis of these patients was extremely poor regardless of the presence or absence of micrometastasis. These data indicate that nodal micrometastasis has clinical significance only in patients with potentially curable oesophageal cancer.

Natsugoe *et al.*[9] have demonstrated that patients without overt nodal metastasis but with newly identified micrometastases have the same poor prognosis as patients with overt metastasis. The same influence of nodal micrometastasis on postoperative survival was observed in the present study; the survival curve of patients without overt metastasis but with micrometastases was similar to that of patients with one to four overt metastatic nodes not accompanied by micrometastasis. Likewise, the survival curve of patients with one to four overt metastatic nodes and concomitant micrometastasis was similar to that of patients with five or more overt metastatic nodes. These findings lead to the possibility of further classifying patients with potentially curable disease (assessed by conventional histological examination) into three groups with different postoperative prognoses, by further assessing micrometastasis to the lymph nodes. Furthermore, these results suggest the need for different strategies in the management of the three patient groups. Oesophageal resection alone may be adequate for patients with neither overt metastases nor micrometastases. Postoperative adjuvant chemotherapy and regular surveillance for tumour recurrence may be indicated for patients with no overt metastasis but with micrometastasis, and for patients with one to four overt metastatic nodes but no micrometastases. However, patients with one to four overt metastatic nodes and concomitant micrometastasis and those with five or more overt metastatic nodes should be considered to have generalized disease that requires frequent postoperative follow-up and intensive multimodality treatment[23].

In conclusion, nodal micrometastasis is an independent, significant predictor of poor survival in patients undergoing curative oesophagectomy. Assessment of nodal status using both histological examination for overt metastasis and immunohistochemical examination for micrometastases is useful for stratifying patients with potentially curable oesophageal cancer to provide them with adequate treatment after oesophagectomy.

Acknowledgements

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Length of the antral segment in pylorus-preserving gastrectomy

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Background: Pylorus-preserving gastrectomy (PPG) has the advantages of preventing dumping syndrome and duodenogastric reflux. However, time was required to reduce symptoms of gastric fullness or to improve food intake after surgery. The aim of this study was to investigate whether the length of the retained antral segment influenced the postoperative symptoms in patients who underwent PPG.

Methods: Thirty patients with early gastric cancer who underwent PPG were divided into two groups according to the length of the retained antrum. In group 1 ($n = 20$) the transection was 1·5 cm and in group 2 ($n = 10$) it was 2·5 cm proximal to the oral edge of the pyloric ring. The subjects were interviewed and examined periodically to assess symptoms, food intake, body-weight and serum nutritional variables. Endoscopy and a radioisotope gastric emptying test were performed 1 year after the operation.

Results: In group 1 gastric fullness after meals was common, resulting in poor food intake and poor recovery of body-weight. A high incidence of food residue in the remnant stomach was found in group 1. With regard to gastric emptying, seven of 20 patients in group 1 and one of ten in group 2 had a delayed emptying curve 1 year after operation.

Conclusion: Group 2 was superior to group 1 in terms of postprandial symptoms, food intake, recovery of body-weight and gastric emptying. The length of the retained antrum may play an important role in the motility of the pyloric ring following PPG.

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Introduction

In 1967, Maki *et al.*[1] first reported pylorus-preserving gastrectomy (PPG) for benign gastric diseases, suggesting that its advantages were in the prevention of the dumping syndrome and protection against mucosal injury of the remnant stomach by duodenal reflux.

A drainage procedure, such as pyloroplasty, in the case of proximal or segmental gastric resection, was not necessary. This principle was based on an experimental study using dogs and which suggested that no additional drainage operation would be required in terms of the intraluminal pressure of the pylorus if the transection were made approximately 1·5 cm proximal to the pyloric ring[2].

In 1991, Kodama *et al.*[3] first described the use of PPG for early gastric cancer based on clinicopathological analyses. PPG is different from conventional distal gastrectomy in that it retains a 1·5-cm length of the pyloric cuff, and does not include suprapyloric lymph node dissection in order to preserve the blood supply and the pyloric branch of the vagus. It is essential that this limited operation should be performed only in patients who do not have metastases to the suprapyloric lymph nodes. Several institutes in Japan have performed PPG in patients with early gastric cancer, and reported some advantages of the procedure[4,5].

The study was undertaken because in a previous report patients who underwent PPG complained of gastric fullness after meals, resulting in poor food intake. As a result, a considerable amount of time was necessary before symptoms of gastric fullness became diminished and food intake improved[6]. Other authors have also reported a high incidence of gastric fullness after meals and long-term retention of food in the residual stomach soon after PPG[7,8]. This feeling of gastric fullness was thought to be associated with delayed gastric emptying due to motility disturbances, although the transection line was made at 1·5 cm from the proximal edge of the pyloric ring. The length of the antral segment that should be retained to improve postoperative symptoms remains unknown. This study was a retrospective investigation into whether the distance of the retained antral segment influenced the postoperative quality of life in patients who underwent PPG.

Patients and methods

Thirty patients with early gastric cancer who underwent PPG between January 1993 and June 1999 were included in this study. They were all younger than 70 years of age when the operation was performed, and had no severe complications. Of the 30 patients, 14 were men and 16 were women. The mean age was 55 (range 36–69) years.

The indications for PPG for early gastric cancer were: (1) age under 70 years, (2) tumour located in the middle of the stomach, (3) mucosal cancer or submucosal cancer if the depth of invasion was limited to the upper layer of the submucosa, and (4) tumour size less than 3·0 cm in diameter.

The preoperative diagnosis of early gastric cancer was made by endoscopic examination according to the dye-spraying method and endosonography.

In the PPG procedure, suprapyloric lymph node dissection was not performed in order to preserve the hepatic and pyloric branches of the vagal nerve, and the distal two-thirds of the stomach was resected while retaining a short segment of antrum. The reconstruction was performed using layer-to-layer anastomosis. In the first 20 patients in this series, the distal stomach was transected at 1·5 cm from the proximal edge of the pyloric ring as described by Maki *et al.*[1] (group 1). In the subsequent ten patients the stomach was transected 2·5 cm from the proximal pyloric edge in an attempt to reduce symptoms of gastric fullness (group 2). All the operations were performed by the same surgeon.

The two patient groups are summarized in *Table 1*. The clinicopathological data were evaluated according to the Japanese classification of gastric carcinoma issued by the Japanese Research Society for Gastric Cancer[9]. There were no significant differences with respect to sex and age distribution, depth of cancer invasion, lymph node metastasis or lymph node dissection.

Table 1 Characteristics of patients who underwent pylorus-preserving gastrectomy for early gastric cancer

	Group 1 (*n* = 20)	Group 2 (*n* = 10)
Sex		
Male	9	5
Female	11	5
Mean(s.d.) age (years)	54(8)	56(6)
Depth of invasion		
m	10	6
sm1	6	1
sm2	4	3
Lymph node metastasis		
n0	19	8
n1	1	2
Lymph node dissection		
D1	16	9
D2	4	1

The subjects were interviewed and examined periodically to assess symptoms, food intake (volume in a single meal), body-weight and serum nutritional variables. Postoperative symptoms were recorded as positive when the patient reported that they were experienced at least once a week during the month immediately preceding the interview. The volume of food intake in a single meal was expressed as a percentage of the normal preillness level and classified into the following three grades: less than 50 per cent, 50–80 per cent and more than 80 per cent. Body-weight changes were expressed as a percentage of normal weight by the formula: body-weight at the time of examination/preillness normal weight × 100. Serum levels of total protein, albumin and total cholesterol were measured as nutritional indices before and after the gastrectomy.

An endoscopic examination was performed by the same endoscopist 1 year after the operation, at which time the presence of food residue, bile regurgitation, reflux gastritis and reflux oesophagitis were recorded. These findings, except for reflux oesophagitis, were evaluated as one of four grades: absent, slight, moderate and severe. The findings of moderate or severe grade were considered positive. The classification of Savary and Miller[10] was used to grade the severity of reflux oesophagitis. The length of pyloric cuff was not measured endoscopically, and no movement of the pyloric cuff or pyloric ring was noted because anticholinergic drugs were injected before examination.

As a measure of the reservoir function[11], the emptying of gastric remnants was calculated using a technetium-99m diethylenetriamine penta-acetic acid (1 mCi)-radiolabelled semisolid test meal (200 g of rice gruel including egg; 151 kcal) 1 year after the operation. All patients ate the test meal over a 5-min period. Immediately after the meal, the patient was placed in front of a γ camera in a standing position and the radioactivity was measured over the whole abdomen for 30 s immediately after the meal (0 min) and 5, 10, 20, 30, 40, 50 and 60 min after the meal. The patients remained in a sitting position at other times during the examination period. Data were stored on disks and processed in a digital computer. Areas of interest corresponding to the gastric remnants were outlined, and the radioactivity was counted on each image and expressed as a percentage of ingested activity.

Statistical analysis was performed using χ^2 and Student's t tests. $P < 0.05$ was considered significant.

Results

Postoperative symptoms

A high frequency of epigastric fullness, nausea, vomiting or gastro-oesophageal regurgitation was found in group 1 up to 1 year after the operation, and there was a significant difference between the two groups at 3 and 6 months. Although the incidence decreased 2 years after the operation, five of 19 patients in group 1 complained of epigastric fullness (*Table 2*).

The dumping syndrome did not occur in either group throughout the follow-up period.

Dietary intake in a single meal

Most patients had a food intake of less than 80 per cent of the preillness level in both groups 3 months after operation. However, a higher proportion of patients had more than 80 per cent of the preillness food intake at 6 and 12 months after the operation in group 2 than in group 1, although there were no significant differences between the two groups. Twenty-four months after the operation, a similar incidence of food intake was found in the two groups (data not shown).

Recovery of lost body-weight

Recovery of lost body-weight in group 2 was significantly better than that in group 1, although no significant difference was found 24 months after the operation (*Fig. 1*).

Serum nutritional variables

Serum levels of total protein, albumin and total cholesterol remained almost completely within normal limits throughout the follow-up period, and no significant differences were seen between the two groups.

Endoscopic findings

One year after PPG food residue was found in 11 patients (55 per cent) in group 1, but only one (10 per cent) of those in group 2 ($P < 0.05$). The incidence of bile regurgitation, reflux gastritis and reflux oesophagitis was similar in the two groups (*Fig. 2*).

Table 2 Postoperative symptoms of epigastric fullness, nausea, vomiting and gastro-oesophageal reflux in patients who underwent pylorus-preserving gastrectomy

	Time after operation (months)			
	3	6	12	24
Group 1	11 of 20	10 of 20	9 of 20	5 of 19
Group 2	1 of 10*	1 of 10*	2 of 10	1 of 9

*$P < 0.05$ *versus* group 1 (χ^2 test)

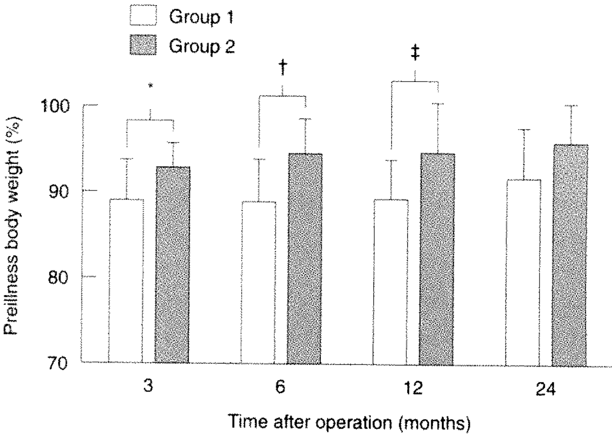


Fig. 1 Change in body-weight in patients who underwent pylorus-preserving gastrectomy. Values are mean (s.d.). *$P < 0.05$, †$P < 0.02$, ‡$P < 0.01$ (Student's t test)

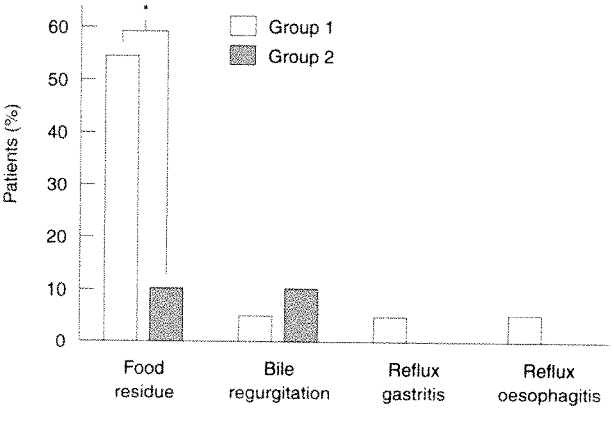
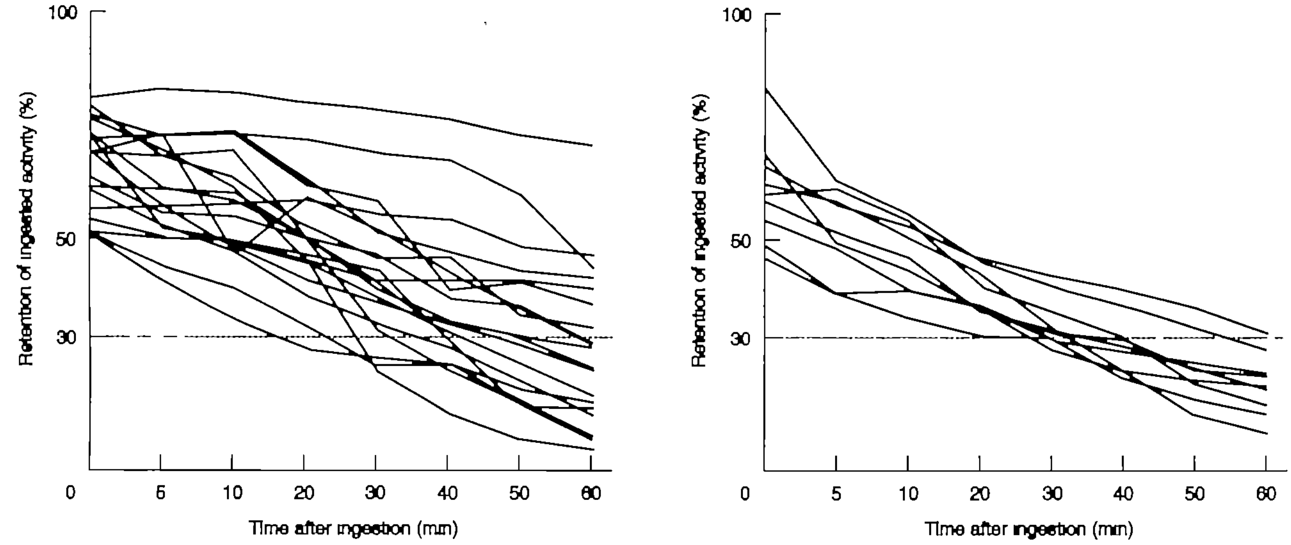


Fig. 2 Endoscopic findings of patients 1 year after pylorus-preserving gastrectomy. *$P < 0.05$ (χ^2 test)

Gastric emptying of the remnant stomach

The emptying curve of the remnant stomach for each of the 30 patients is shown in *Fig. 3*. The mean retention rate of



a Group 1 **b** Group 2

Fig. 3 Gastric emptying curves of an isotope (technetium-99m diethylenetriamine penta-acetic acid)-labelled semisolid meal in patients in group 1 (**a**) and group 2 (**b**) 1 year after pylorus-preserving gastrectomy. The dotted line indicates the retention rate above which emptying was considered to be delayed

the test meal in five healthy volunteers was 20·3 per cent of the ingested activity 60 min after ingestion. Considering this retention value, the authors defined a retention rate of more than 30 per cent as delayed gastric emptying. In group 1, the retention rates of seven patients showed delayed emptying. Delayed emptying was noted in only one patient in group 2 (retention rate 30·4 per cent).

Discussion

In a previous study[6], PPG had the advantages of preventing dumping syndrome and protecting against duodenogastric reflux. However, a significant time period was required for improvements in postprandial epigastric fullness and food intake to occur.

The sensation of epigastric fullness is thought to be based on the relationship between gastric emptying, the size of the remnant stomach (retention capacity), and such conditions of food intake as volume, speed and food constituents.

Maki *et al.*[1,2] reported in an experimental study that transection of the stomach 1·5 cm proximal to the pylorus maintained a functioning sphincter. A more distal transection weakened the sphincter and a more proximal transection gave rise to frequent antiperistalsis or spastic contraction of the retained antrum, which resulted in delayed emptying of the stomach. Holle *et al.*[12] suggested that division of antral intramural nerves led to a delay in gastric emptying.

In a clinical study in patients with gastric ulcer, Maki *et al.*[1] selected the same antral transection site as that in the animal studies and obtained satisfactory results. No delayed emptying was noted using the test meal prepared by mixing 100 g barium sulphate powder with 150 g rice gruel. Liavag *et al.*[13] also obtained satisfactory results in patients with gastric ulcer using the same procedure. On the other hand, Griffith[14] reported that seven of 20 patients with duodenal ulcer who underwent selective vagotomy plus suprapyloric antrectomy complained of symptoms of gastric stasis.

It is not certain whether 1·5 cm measured from the antral cuff is reasonable for human subjects in terms of gastric emptying. In the present study better results were obtained in patients who underwent PPG with transection 2·5 cm proximal to the pyloric ring (group 2) than in patients with transection 1·5 cm proximal to the pylorus (group 1). The size of the remnant stomach, grade of vagal denervation of the remnant stomach for lymph node dissection, and preservation of the hepatic and pyloric nerves were similar between the two groups, and all operations were performed by the same surgeon.

The main reason for epigastric fullness and poor food intake was thought to be delayed gastric emptying. In fact, three patients in group 1 with epigastric fullness 5 years after operation had their symptoms relieved by endoscopic and fluoroscopic balloon dilatation of the pyloric ring, which also improved their delayed gastric emptying.

It remains to be elucidated why pyloric motility with a longer retained antrum after PPG is superior to that of PPG with a short antrum. No clinical studies of the motor function of the pylorus in terms of the length of the retained antrum after PPG exist.

In conclusion, PPG with transection 2·5 cm proximal to the pyloric ring was superior to that with transection of 1·5 cm in terms of postprandial symptoms, food intake, recovery of body-weight and gastric emptying. The length of the retained antrum plays an important role in the motility of the pyloric ring following PPG.

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Original article

Long-term results of antireflux surgery indicate the need for a randomized clinical trial

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Background: Well conducted, comparative trials of laparoscopic *versus* open antireflux surgery with an adequate patient enrolment are few and they do not demonstrate obvious advantages for the laparoscopic approach except for a marginal gain in shorter hospital stay. The aim of this study was to compare the effectiveness of laparoscopic and open procedures.

Methods: Two unselected groups of 230 patients were identified through a register of all inpatient public care in Sweden. Outcomes of laparoscopic and open antireflux surgery were compared using a disease-specific questionnaire 4 years after operation.

Results: Failure and dissatisfaction were significantly more common in the laparoscopy group than among patients having conventional open surgery. Treatment failure rates were 29·0 and 14·6 per cent respectively ($P = 0{\cdot}004$). Dissatisfaction rates were 15·0 and 7·0 per cent respectively ($P = 0{\cdot}005$). There was no other questionnaire item for which the proportion of failures differed significantly between the two groups.

Conclusion: This study does not support the presumption that laparoscopic antireflux surgery is to be preferred to the open procedure. It is strongly recommended that a randomized controlled trial be conducted.

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Introduction

There have been major changes in the treatment of gastro-oesophageal reflux disease (GORD) during the past decade. At the same time as proton pump inhibitors (PPIs) were proven to be an effective therapy for most patients suffering from GORD[1], the frequency of antireflux surgery increased. Moreover, the laparoscopic technique for antireflux surgery was introduced in 1991 and in many countries it soon replaced the open procedure as the method of choice[2,3]. In Sweden the annual number of antireflux procedures has tripled since 1987[2]. Today, approximately 1300 patients are operated on each year, and 85 per cent of them have a laparoscopic procedure[4]. Long-term follow-up studies that compare the effectiveness of the two different techniques have not been undertaken. Both surgeons and patients seem to prefer the laparoscopic technique[3,5,6] and there could be logistical and ethical problems with implementing a formal prospective randomized study.

The goal of antireflux surgery is resolution of all symptoms of gastro-oesophageal reflux with negligible side-effects and no further need for medical therapy[7,8]. To evaluate the outcome of antireflux surgery it is therefore paramount to ask the patients whether or not they are satisfied and symptom-free. Exclusion of heartburn, which is the cardinal symptom of GORD, correlates well with postoperative return to normal of 24-h pH monitoring[9]. Several investigators have proposed disease-specific questionnaires as a tool for follow-up surveys after antireflux surgery[8–10].

The purpose of this study was to assess the long-term results of the laparoscopic technique compared with the open procedure using a posted questionnaire.

Patients and methods

Data were collected from the Centre for Epidemiology at the Swedish National Board of Health and Welfare. The Centre for Epidemiology administers a register of all inpatient public hospital care in Sweden[4]. The validity of the register for antireflux surgery has been verified in a previous study[2].

From 1 January 1995 to 31 December 1996, 2464 antireflux procedures were performed. Of these 1544

(62·7 per cent) were done laparoscopically. To make the study groups uniform, those hospitals were selected in which more than 50 patients had been operated on by one of the techniques. There were five hospitals where 660 laparoscopic procedures were done (median 60, range 50–411) and four hospitals that performed predominantly open surgery, accomplishing 358 procedures (median 66, range 50–185). One hospital was represented in both groups.

Table 1 Study groups and reasons for exclusion

	Open procedure	Laparoscopic approach
No. of patients identified in register	235	225
No. who died	2	1
No. who moved or could not be traced	3	5
No. excluded		
Combination with other major abdominal procedures	10	1
Previous antireflux surgery	16	0
Not able to answer (age, cerebral disease)	1	1
Final sample size	203	217
No. responding to questionnaire	185	200
Response rate (%)	91·1	92·2
Women (%)	47·0	39·5*
Mean age (years)	57·8	53·5†
Mean BMI	26·3	26·3‡

Median follow-up in both groups was 4 (range 3·4–5·5) years. BMI, body mass index. *$P = 0{\cdot}135$ (χ^2 test), †$P = 0{\cdot}0001$ (t test), ‡$P = 0{\cdot}95$ (t test)

It was proposed that the open and laparoscopic techniques were equally effective in controlling symptoms and providing patient satisfaction. The success rate was estimated to be 85–95 per cent[11]. Sample sizes of approximately 180 patients were necessary to detect a difference of 10 per cent in failure rate in a two-tailed test with a significance level of 5 per cent and 90 per cent power. The response rate was estimated to be 80–90 per cent. Two random samples of approximately 230 patients in each were thus identified for study purposes. The number of patients excluded and the different reasons for exclusion are given in *Table 1*.

The study protocol was approved by the local ethics of science committee at Uppsala University. The Centre for Epidemiology gave permission to obtain the patients' identities and addresses.

A questionnaire designed to detect typical symptoms of GORD and to identify postoperative side-effects of antireflux surgery was posted to all patients (*Table 2*). The choice of participation in this study was free and no economic compensation was given. Non-responders received a second survey. The usefulness of the questionnaire had been tested on 136 patients before the study was undertaken. The main endpoints were treatment failure and patient satisfaction. Treatment failure was defined by the presence of one or more of three criteria: (1) a new antireflux procedure had been required to control symptoms or to relieve side-effects; (2) medication was taken at least once a week specifically to relieve heartburn or acid regurgitation; and (3) patient dissatisfaction with the result of the operation.

Table 2 The questionnaire

All questions regarding symptoms refer to how you have felt during the past month.	
Do you suffer from heartburn or acid regurgitation?	(No/Not daily/1–5 times daily/> 5 times daily)
Do you take any medication to relieve heartburn or acid regurgitation?	(No/Seldom/At least once a week/Daily)
If you take daily medication, please specify drug(s) and dose.	
Do you have difficulty swallowing liquids?	(Never/Not daily/1–5 times daily/> 5 times daily)
Do you have difficulty swallowing solid food?	(Never/Not daily/1–5 times daily/> 5 times daily)
Do you have difficulty belching?	(Yes/No/Not able to)
If you have to vomit, do you feel it is more difficult after than before the operation?	(Yes/No/No opinion)
Do you have problems with gas bloat or flatulence?	(Never/Seldom/At least once a week/Daily)
Which abdominal symptom or complaint do you experience as the most bothersome?	
Do you have any complaints regarding your scars?	(Yes/No)
If yes, please explain.	
Have the symptoms or complaints that made you undergo the operation improved?	(Yes, definitely/Yes, to some extent/No)
Would you recommend this operation to patients with similar symptoms to those you suffered from?	(Yes/No)
Sometimes the first operation is ineffective, or the symptoms recur, and another operation is necessary. Have you had this kind of operation more than once?	(Yes/No)
In summary, how would you rate your satisfaction with the results of the operation?	(Very satisfied/Satisfied/Dissatisfied/Very dissatisfied)
If you are dissatisfied, please explain why.	
Please give your height and weight.	

Table 3 Results for selected questionnaire items

	Laparotomy group (*n* = 185) (%)§	Laparoscopy group (*n* = 200) (%)§	*P*‡
Effectiveness of antireflux procedure			
No improvement	2·0	6·0	0·10
Revisional surgery	5·4	6·0	0·63
Acid regurgitation (more than once daily)	3·8	8·6	0·07
Heartburn (more than once daily)	6·0	11·0	0·08
Medication*	8·7	19·5	0·02
Failure†	14·6	29·0	0·004
Dissatisfied	7·0	15·0	0·005
Procedure-related side-effects			
Difficulty swallowing food (more than once daily)	9·8	8·0	0·74
Difficulty swallowing food (more than five times a day)	1·6	2·0	
Difficult or unable to belch	33·2	29·0	0·33
Gas bloat, flatulence (daily complaints)	27·7	31·8	0·88
Complaints regarding scar	13·6	7·5	0·02
Would recommend the operation	92·3	92·0	0·99

*Medication taken at least once a week specifically to relieve heartburn or acid regurgitation. †An operation was defined as a failure if one or more of three criteria were present: reoperation, medication taken at least once a week specifically to relieve heartburn or acid regurgitation, and dissatisfaction with the overall result. ‡Logistic regression. §All patients did not respond to all questions

Statistical analysis

Several questions had possible responses that were dichotomized into 'failure' and 'success' for comparative purposes. Comparison of questionnaire items between the groups was conducted using a logistic regression with the covariates of sex, age and body mass index (BMI). The Bonferroni correction was used to control the overall type I error rate at 0·05. Comparison of age, sex and BMI between the groups was performed with *t* tests and the χ^2 test.

Results

Failure and dissatisfaction were significantly more common in patients in the laparoscopy group than among those in the laparotomy group (*Table 3*). Treatment failure rates were 29·0 and 14·6 per cent respectively (*P* = 0·004). The dissatisfaction rates were 15·0 and 7·0 per cent respectively (*P* = 0·005).

An estimated 19·5 per cent of patients in the laparoscopy group and 8·7 per cent in the open group stated that they used medication at least once a week specifically to relieve heartburn or acid regurgitation (*P* = 0·02). Most of them used medication every day; 74·5 per cent used PPIs.

Table 4 Frequency of the most troublesome gastrointestinal symptoms

	Laparotomy group (*n* = 185)	Laparoscopy group (*n* = 200)	All patients (*n* = 385)
Gas bloat or flatulence	74	79	153 (39·7)
Epigastric or substernal pain	18	19	37 (9·6)
Heartburn	5	15	20 (5·2)
Dysphagia	5	3	8 (2·1)
Diarrhoea or constipation	8	6	14 (3·6)
Other symptoms	18	27	45 (11·7)
No symptom or no response	72	75	147 (38·2)

Values in parentheses are percentages. The sum of frequencies is larger than the number of patients because some patients listed two symptoms

Only 2·1 per cent (eight patients) considered dysphagia to be the most troublesome postoperative symptom (*Table 4*). Even among patients who had daily episodes of difficulty in swallowing, gas bloat and flatulence were more often considered to be the worst complaint.

Complaints related to scar tissue were reported by 7·5 and 13·6 per cent, more commonly in the laparotomy group (*P* = 0·02) (*Table 3*). However, the symptoms were often minor (e.g. scratching sensation, mild hyperaesthesia, dissatisfaction with cosmetic appearance). Incisional hernia was suspected in four patients in the laparoscopy group and in seven in the laparotomy group.

The most common reasons for dissatisfaction were lack of improvement (18·6 per cent), relapse (34·8 per cent) and troublesome side-effects such as gas bloat (23·3 per cent).

Adjustment was made for three confounding factors (age, sex and BMI), but the difference between the groups was not significant for any of these variables. Neither age nor sex had a significant influence on outcomes of the different items. However, BMI did seem to have an impact on outcome: as BMI increased, the more satisfied was the patient with his or her experience after operation. The correlation was statistically significant (*P* = 0·0006), but the magnitude of the correlation was small with a Spearman correlation coefficient of −0·14, and BMI was almost identical in the laparoscopic and open groups.

Discussion

The main findings in the present study were that patients who had an open procedure experienced treatment failure less often and were significantly more satisfied with the overall result than those operated on laparoscopically.

Since its introduction in 1991 the laparoscopic technique has replaced open antireflux surgery as the method of choice[2,3]. Less surgical trauma, reduced pain, shorter hospital stay and sick leave, and cosmetically more acceptable scars are some of the proposed advantages[12–14]. It is assumed that laparoscopic surgery will give at least equal results to open procedures. Many studies report excellent short-term results after laparoscopic antireflux surgery[12,13,15,16], but a fair comparison of laparoscopic and open techniques is difficult given the constraints of the non-randomized research methodology used in almost all of these studies[11,17,18]. To the authors' knowledge the results from only five controlled randomized trials comparing the outcome after the two techniques have been published. The Dutch multicentre study was discontinued because of a high incidence of early dysphagia in the laparoscopy group[19]. In a Swedish study with blind evaluation of recovery and discharge period, patients in both groups stayed in hospital for a median of 3 days after operation and no significant differences were found in the duration of sick leave[20]. Good short-term results after both laparoscopic and open procedures have been reported from Finland in three prospective randomized studies, but the number of patients in each study was small[21–23].

It is also a problem that the criteria for evaluating success or failure are not uniform[3,8]. To equate reflux control with success rate may give a false impression[6,7]. The number of patients still on antireflux medication[5,10,12,13,16,17] is often not stated but, if reported, continuous medical therapy in about 6–8 per cent is usual[6,11,24]. Even patients with objectively demonstrated anatomical failure of the fundic wrap often do well on PPIs[5]. The definition of failure in the present study was rather demanding, but was defined in order to achieve the goals of antireflux surgery. For a disease where an alternative and often equally effective medical therapy exists[25], the goal needs to be an optimal surgical result, and patient satisfaction is therefore crucial. After all, most patients who agree to undergo surgery do so because of troublesome symptoms and not because of objective signs, such as endoscopic findings or the results of 24-h pH monitoring. Indiscriminate use of acid suppression therapy does not necessarily represent a technically failed antireflux procedure, but this was regarded as a treatment failure because cessation of medication to suppress the symptoms of GORD is an important aim of surgery. The questionnaire was also designed to detect medication used specifically to suppress reflux symptoms. Moreover, because the questionnaires in the present study were handled anonymously and confidentially, and did not involve any of the authors' patients, there is no danger of the kinds of bias that may result when researchers investigate their own patients.

The Centre for Epidemiology administers a complete nationwide register, and the two different samples of the study population were demographically similar regarding sex and BMI. The open procedure was often recommended for older patients with cardiopulmonary impairment and for those who had previously had an operation on the upper abdomen. A somewhat higher mean age is therefore to be expected in the open group. This may also explain why all the patients who had had an earlier antireflux operation were found in the laparotomy group. In 1996 and 1997 it was not common in Sweden to offer revisional surgery laparoscopically.

Almost every antireflux procedure done in Sweden is, in principle, either a Nissen or a Toupet fundoplication. The classification number is different for laparoscopic and open procedures, but is the same regardless of total or partial fundoplication. Because the authors had no information regarding the hospital in which a particular patient had undergone operation, it was not possible to differentiate between the surgical procedures. Other factors also influence the long-term results, in particular the indication for operation, the selection of different techniques, differences in hospital routines and the experience of the surgeon. These circumstances could not be adjusted for by any means other than a large sample size.

In the laparotomy group 93·0 per cent of patients declared they were satisfied with the outcome and 94·0 per cent reported good reflux control 4 years after operation. These results may be considered good as they are comparable to reports from specialized centres[11,24–27]. The results in the laparoscopic group, however, were worse than those suggested by most of the literature[12,13,15–17], but they were not extreme[5,28,29]. At 2-year follow-up after laparoscopic fundoplication, Soper and Dunnegan[5] reported that 26 per cent of patients had symptoms suggestive of persisting gastro-oesophageal reflux. Anatomical failure of the procedure was documented in 7 per cent, and surgical revision was required in 2·8 per cent. The incidence of revisional surgery after a primary laparoscopic approach is usually about 2–6 per cent at short-term follow-up[11]. Most remarkably, the Adelaide group noted that 12·9 per cent of patients required reoperation in a 5-year follow-up of 178 consecutive patients operated on laparoscopically[29].

The long learning curve of laparoscopic antireflux surgery may be a confounding factor. However, laparoscopic antireflux surgery had been performed for more than 3 years in Sweden and 950 procedures had been accomplished before the study period[2]. In addition, the patients were selected only from those hospitals with high activity in laparoscopic antireflux surgery. Even though this was an inclusion criteria of the study, it may also be a bias. An increasing incidence of antireflux operations may tend to lower the threshold for accepting patients for surgery[3,17,30]. In their enthusiasm for the new approach, surgeons undertaking laparoscopic procedures may have operated on patients with less convincing symptoms of GORD. It was a trend during the 1990s to focus more on technical skills in laparoscopic handicraft than on the experience of antireflux surgery, and laparoscopic surgeons at many hospitals took over antireflux surgery from specialized thoracic and oesophageal surgeons[6].

Initially surgeons may have found it difficult to accomplish an equivalent antireflux procedure by means of the laparoscopic compared with an open approach[14]. 'Minor' adjustments of the antireflux procedure could have been made, such as omission of hiatal repair and insufficient mobilization of the gastric fundus. If so, this may also have had an impact on outcome after laparoscopic antireflux surgery.

It is unlikely that disappointment with the minimally invasive procedure was the reason for dissatisfaction as this should have waned 4 years after operation. Furthermore, disappointment cannot explain why patients in the laparoscopy group reported more frequent reflux symptoms and required more medication to relieve such symptoms. The dissatisfied patients usually complained about lack of improvement, relapse and troublesome side-effects. Nevertheless, as many as 92·0 per cent of the patients in the laparoscopic and 92·3 per cent in the open group would recommend the procedure for patients with similar symptoms. This may be an indication that the operation had, after all, improved their situation. Dysphagia is one of the most troublesome complications of antireflux surgery[19,31]. The results of the present study indicate that persistent dysphagia is not a common complaint. Interestingly, 39·7 per cent of all the patients regarded gas bloat or increased flatulence as the most troublesome postoperative abdominal symptom.

In conclusion, this study does not support the presumption that laparoscopic antireflux surgery is to be preferred to an open procedure. It suggests that patients do not derive significant benefit from having the antireflux procedure performed laparoscopically. It is strongly recommended that a randomized controlled trial be conducted.

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Endoscopic ultrasonography in the diagnosis and management of suspected upper gastrointestinal submucosal tumours

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Background: 'Submucosal' lesions in the upper gastrointestinal tract are often difficult to evaluate. Endoscopic ultrasonography (EUS) provides high-quality information about the nature of these lesions and may assist management. This study assessed the use of EUS in the evaluation and management of upper gastrointestinal submucosal tumours.

Methods: Forty-four consecutive patients were referred with suspected upper gastrointestinal submucosal lesions for EUS. All examinations were performed by one of two experienced endosonographers.

Results: Most patients were referred for EUS with a suspected gastrointestinal stromal tumour. The pre-EUS diagnosis did not correlate with the EUS diagnosis in 25 of 44 patients. Pathological correlation was possible in 16 patients, and the EUS diagnosis was confirmed in each case. Based on the findings at EUS, 12 patients underwent resection. Pathology confirmed the ultrasonographic findings in these patients. Follow-up EUS to monitor lesions was recommended in a further three patients.

Conclusion: EUS is safe and provides useful information in many patients with suspected submucosal tumours. EUS may reveal unsuspected findings and can increase physician certainty, allowing accurate diagnosis and facilitation of the management process.

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Introduction

Gastrointestinal submucosal or intramural lesions are either discovered coincidentally in patients undergoing routine upper gastrointestinal endoscopy or may be the cause of symptoms such as abdominal pain or bleeding. Endoscopically they are seen as a bulge into the lumen, usually covered by normal looking mucosa, and their exact nature may be difficult to diagnose accurately from endoscopy alone. Endoscopic biopsies usually reveal normal or non-specifically inflamed superficial mucosa, while fine-needle aspiration or core-needle biopsy may be misleading and does not usually allow the clinician to accurately distinguish benign from malignant lesions. Once discovered, the further management of patients with these lesions is often uncertain, with patient and physician anxiety resulting in either frequent endoscopic monitoring or surgical resection.

Endoscopic ultrasonography (EUS) can clearly demonstrate the intestinal wall as a series of distinct layers of differing echogenicity and can visualize structures adjacent to the intestinal wall. As such, it can distinguish intramural lesions from extrinsic compression reliably, can tell solid from cystic or vascular lesions, and can often accurately diagnose the nature of submucosal tumours on the basis of their wall layers of origin and echocharacteristics. EUS alone cannot substitute for histology and cannot reliably tell whether a lesion is benign or malignant.

This study presents experience of using EUS in the assessment of patients referred with suspected upper gastrointestinal submucosal lesions and the role of EUS in determining further management of these patients.

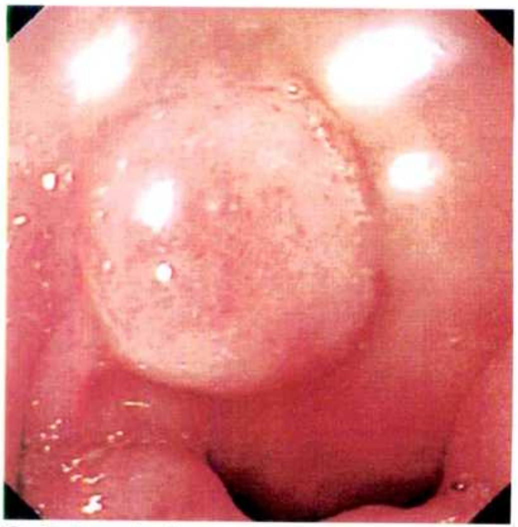
Patients and methods

Between January 1999 and March 2001, 44 consecutive patients were referred for EUS for further evaluation of a suspected submucosal lesion discovered at upper gastrointestinal endoscopy. For each patient the following information was recorded: demographics, symptoms, indi-

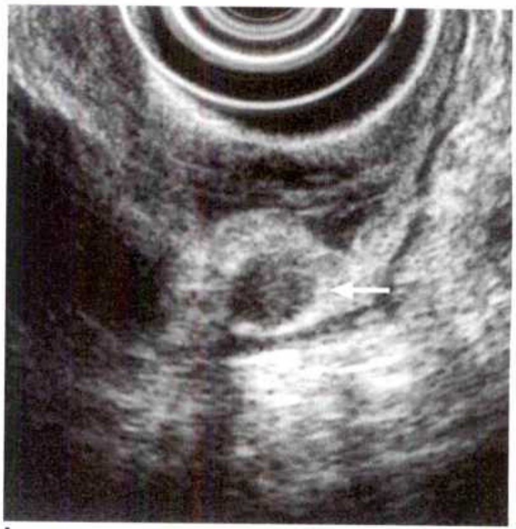
Table 1 Diagnosis based on endosonographic findings ($n = 44$)

Lesion	No.
Gastrointestinal submucosal tumour	12
Inflammatory polyp	6
No lesion seen	4
Vascular lesion	5
Ectopic pancreas	4
Carcinoid	2
Lipoma	3
Other*	8

*These included a cyst, granular cell tumour, pericardial effusion, lymphadenopathy (two patients), gallbladder, submucosal metastases (known breast cancer) and a hammartoma



a Endoscopic view



b Sonographic view

Fig. 1 **a** Endoscopic view of a 1-cm polypoid lesion in the first part of the duodenum. Biopsies showed mild non-specific inflammation. **b** Endoscopic ultrasonography revealed a homogeneous, discrete, hypoechoic lesion in the third layer (arrow) with submucosa also behind the lesion and normal muscularis propria. The features are those of a carcinoid tumour, confirmed on endoscopic resection

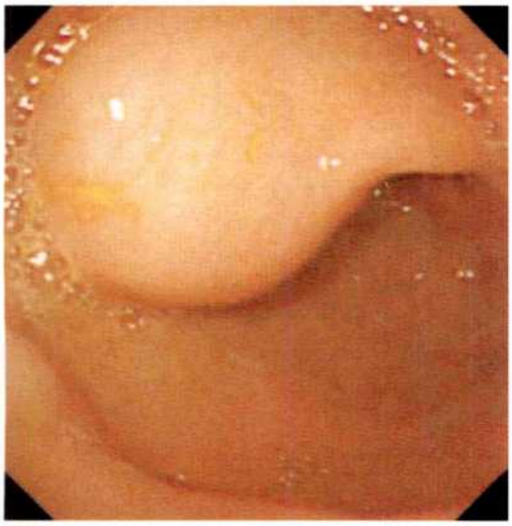
cation(s) for endoscopy and EUS, endoscopic findings and provisional diagnosis before referral for EUS. At EUS, the following features were sought and recorded: site and size of lesion, wall layer(s) involved, internal echotexture, outer margins, evidence of invasion beyond the intestinal wall and presence of adjacent lymph nodes or other abnormalities. Pathological correlation with resected specimens was made where possible. For lesions that were not resected outcome was determined by clinical follow-up.

In all patients, careful upper endoscopy was performed followed by EUS using mechanical radial echoendoscopes at a scanning frequency of 7·5 or 12 MHz (Olympus GF-UM200 or GF-UM10; Olympus, Tokyo, Japan). High-frequency catheter probes were not available at the time of this study. All procedures were performed on an outpatient basis, by one of two experienced endosonographers (I.D.P., J.P.) using conscious sedation (intravenous midazolam with or without pethidine). Written informed consent for EUS was obtained from all patients.

Results

Of the 44 patients, 23 were women and the mean age was 62 (range 26–88) years. The initial endoscopy was performed for a number of reasons, including dyspepsia/pain, upper gastrointestinal bleeding, dysphagia and anaemia. Most patients were referred for EUS with a suspected gastrointestinal stromal tumour ($n = 17$ (confirmed in 9)) or suspected malignancy ($n = 7$). While the most common endosonographic diagnosis was a gastrointestinal submucosal tumour (*Table 1*) the EUS diagnosis did not correlate with the initial endoscopic diagnosis in 25 patients, most often because EUS discovered alternative diagnoses for lesions thought endoscopically to represent stromal tumours.

Pathological correlation was possible in 16 patients and the EUS diagnosis was confirmed in all. In four of these patients, lesions underwent endoscopic resection after EUS, whereas eight patients underwent surgical removal of the lesion. No malignant tumours were found in patients undergoing resection. One large gastrointestinal stromal tumour that contained cystic areas and an irregular outer border on EUS underwent resection, but on review of the pathology was felt to be benign. Follow-up EUS 1 year later revealed no evidence of recurrence. One patient,



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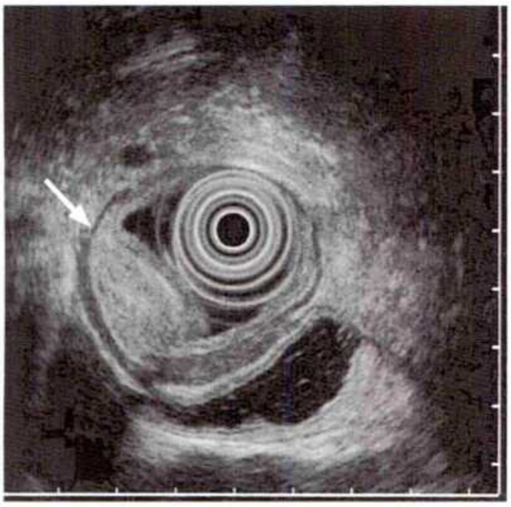
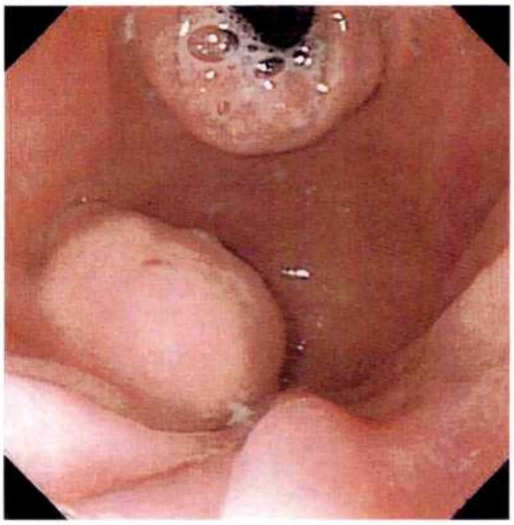
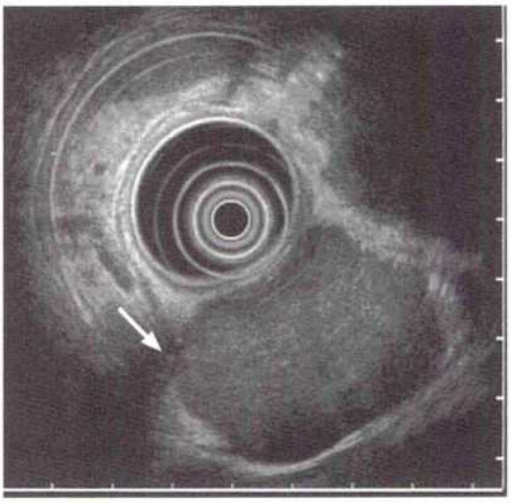


b Sonographic view

Fig. 2 **a** Endoscopic view of a smooth bulge in the antrum of a patient undergoing endoscopy for dyspepsia. A gastrointestinal stromal tumour was suspected but endoscopic ultrasonography (**b**) revealed a discrete, hyperechoic lesion arising from and confined within the submucosa (arrow). The muscularis propria is not involved and the features are those of a lipoma



a Endoscopic view



b Sonographic view

Fig. 3 **a** Endoscopic view of a polypoid lesion in the gastric fundus of a patient presenting with melaena. **b** Endoscopic ultrasonography confirmed a 4-cm hypoechoic and homogeneous lesion arising from the fourth layer (muscularis propria, arrow) with no extension beyond the stomach. Surgical resection confirmed a benign gastrointestinal stromal tumour

who presented with bleeding, underwent argon plasma coagulation after EUS showed features consistent with a haemangioma.

No malignancies have been discovered during clinical follow-up (mean 16·4 months) of the 31 patients whose lesions were not treated. Of these, further EUS surveillance was recommended in three (one granular cell tumour, two gastrointestinal stromal tumours), while the remainder were felt to not require further follow-up with EUS. Examples of 'submucosal' lesions and corresponding findings at EUS are shown in *Figs 1–3*.

Discussion

'Submucosal' tumours pose a diagnostic challenge, often requiring resection to establish the exact diagnosis. Lesions not resected are often followed by regular endoscopy to ensure that they are not enlarging. With the development of EUS, it is possible to distinguish intramural lesions from extrinsic compression[1–3]. EUS also provides information with respect to the layer(s) of origin, the echotexture and margins of a lesion. Consequently, EUS can be useful as a diagnostic tool for suspected submucosal tumours[4–7]. Gastrointestinal stromal tumours (e.g. leiomyomas) are well demarcated hypoechoic lesions that arise from the second or fourth layers (muscularis mucosa or muscularis propria). In contrast, ectopic pancreas is heterogeneous with indistinct margins and arises in the third and possibly fourth layers[8] (submucosa and muscularis propria), while lipomas and liposarcomas are characteristically hyperechoic, arising from the third layer (submucosa)[9]. In contrast, tubular anechoic structures in the third layer are typical of vascular lesions such as varices.

In the present series, the procedure was technically successful in all cases. In four patients, no pathological lesion could be confirmed at endoscopy or EUS, and the patient was reassured. In four the submucosal tumour was in fact the result of an extrinsic compression or indentation: gallbladder impression on the antrum (one), mediastinal lymphadenopathy (two) and pericardial effusion (one). Seventeen patients were referred with a suspected gastrointestinal stromal tumour; this was confirmed in nine but eight had an alternative endosonographic diagnosis, for example lipoma, hyperplastic polyp or ectopic pancreas. Computed tomography (CT) was performed in only six of the 44 patients (three before referral for EUS and in the three patients with extrinsic compression from mediastinal nodes or pericardial effusion). While helical CT has improved the imaging of the gastrointestinal wall layers, it is still inferior to EUS for assessment of submucosal lesions and is not used routinely.

EUS can be useful in assisting the management of submucosal tumours[10]. The depth of a lesion is important when deciding on suitability for possible removal by submucosal resection. EUS can accurately delineate depth of penetration, thus allowing safe endoscopic removal of lesions[11–15]. Whether submucosal tumours can be distinguished as benign or malignant by EUS is still controversial[9,16]. However, certain features on EUS may be more suggestive of malignancy. These include size greater than 3–4 cm, poorly defined or irregular margins, presence of internal echogenic foci or cystic spaces, adjacent lymphadenopathy and rapid growth rate at follow-up EUS[7,17,18].

In this study EUS made a difference to patient management. In over half the patients, the presumed diagnosis was not confirmed at EUS. Following EUS, four lesions were found to be suitable for endoscopic resection, while eight patients were referred for surgical resection of the lesion. All of these patients had a gastrointestinal stromal tumour; six had presented with gastrointestinal bleeding and the other two with symptoms attributable to the size of the lesion. In contrast, patients with extrinsic indentation from an adjacent, but otherwise normal, structure (e.g. gallbladder) were reassured and discharged from further follow-up. Those with extrinsic compression from mediastinal lymphadenopathy or pericardial effusion were referred for further investigation. Those with a submucosal tumour were either reassured or recommended to undergo periodic surveillance, depending on various factors including patient or referring physicians' preference, size of lesion and comorbidity.

A number of other studies has looked at the clinical implications and impact of EUS. Taken together, they suggest that the use of EUS for evaluating submucosal tumours will generally decrease the number of further investigations required[5,10,19]. However, well designed prospective studies of the economic impact of EUS in the management of patients with these lesions are still awaited[20].

In this study the follow-up period was relatively short (mean 16·4 months) and may not be long enough to be reassured of the benign nature of the lesions followed up clinically. The results of long-term EUS surveillance studies to monitor possible changes in submucosal tumours are still awaited.

In conclusion, EUS can assist in the accurate diagnosis of suspected submucosal lesions, frequently yielding previously unsuspected findings and providing supporting information about the nature of lesions, the likely need for endoscopic or surgical resection, and the need for further endoscopic follow-up. This information may allay patient anxiety, increase physician certainty and reduce the need for further intervention.

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Abnormal expression of E-cadherin and β-catenin may be a molecular marker of submucosal invasion and lymph node metastasis in early gastric cancer

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Background: Impaired expression of E-cadherin and α- and β-catenin is frequently observed in several human cancers. The aim of this study was to examine immunohistochemical expression of these adhesion molecules, focusing on early gastric carcinomas, and to investigate differences between differentiated and undifferentiated gastric cancer at the early phase of carcinogenesis.
Methods: Immunohistochemical staining of E-cadherin and α- and β-catenin was performed using specimens from 143 patients with early gastric cancer.
Results: Abnormal E-cadherin and β-catenin staining correlated with depth of tumour invasion in differentiated-type tumours. In contrast, abnormal staining was frequently found even in intramucosal carcinoma of undifferentiated-type tumours, suggesting an apparent difference in the onset of E-cadherin–catenin complex abnormality between the two cancer types. Absent staining of β-catenin was associated with lymph node metastasis. Multivariate analysis revealed abnormal E-cadherin expression as an independent factor that correlated with submucosal invasion in early gastric cancer.
Conclusion: Abnormal E-cadherin expression is a possible marker of submucosal invasion in differentiated-type early gastric cancer and absent β-catenin staining could be used as a predictor of lymph node metastasis in both types.

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Introduction

Gastric carcinomas have been classified by Laurén into intestinal and diffuse types[1]. These two histological types correspond roughly to differentiated and undifferentiated types, according to the degree of glandular formation by the tumour cells, as proposed by the Japanese Research Society for Gastric Cancer[2]. Characteristics such as invasiveness, tendency toward metastasis and prognosis have been widely reported to differ between the two tumour types. Differentiated-type carcinoma is associated with fewer lymph node metastases, less frequent recurrence and a more favourable prognosis than undifferentiated-type carcinoma[1].

The cadherin–catenin complex, which consists of E-cadherin and α-, β- and γ-catenin, has been implicated in cell–cell adhesion and maintenance of normal tissue architecture[3]. E-cadherin interacts at a conserved cytoplasmic domain with the cytoskeleton via associated cytoplasmic molecules, α-, β- and γ-catenin[4,5]. Loss of function in any one of these components is believed to result in loss of cell–cell adhesion and contribute to neoplasia[6–10]. Abnormalities in expression and function of the adhesion complex, specifically in E-cadherin and α- and β-catenin, have been found in a number of tumours and cell lines[11–17]. Previous studies have shown a relationship between expression of the adhesion complex and Laurén's classification, and reported that abnormal expression of the cadherin–catenin complex tends to occur more frequently in diffuse-type carcinoma than intestinal-type carcinoma[13,14,18,19].

Recently, the proportion of early gastric carcinoma in Japanese patients has increased steadily to approximately 40 per cent[20]. The prognosis after surgical treatment for early gastric carcinoma is extremely favourable, with 5-year survival rates exceeding 90 per cent[20,21]. However, some tumours are highly aggressive and recur in the form of distant organ or lymph node metastases. Lymph node metastasis is regarded as a significant factor that influences prognosis and selection of treatment modalities even in patients with early gastric carcinoma[21–24].

Preoperative assessment of the presence of lymph node metastasis and the depth of wall invasion is critical for determining appropriate therapies for early gastric cancer. Numerous studies have attempted to predict lymph node metastasis and the depth of wall invasion before initial treatment of patients with gastric cancer. Several conventional clinicopathological factors, such as tumour staging, lymphatic vessel invasion and penetrating type, are known to correlate with lymph node metastasis[21,25,26]. However, these factors cannot be used for predicting lymph node metastasis at the preoperative stage. Previous groups have therefore sought to identify biomarkers for predicting lymph node metastasis[11,25,27]. Since lymph node metastases are present in only 3–5 per cent of mucosal tumours, but in 10–25 per cent of submucosal tumours[1], it is also important to assess invasion depth before operation in early gastric cancer. Radiological and endoscopic examinations are extremely useful for non-invasive diagnosis during pretreatment staging. Endoscopic ultrasonography is particularly useful for assessing the depth of invasion[22,23,28]. However, it cannot differentiate precisely between intramucosal and submucosal cancer, because of the presence of limited infiltration into the submucosa. Therefore, biological markers that accurately assess the depth of tumour invasion into the submucosa could facilitate detection of submucosal cancer and improve selection of treatment.

The primary goals of this study were: (1) to assess changes in adhesion complex expression during the early phase of gastric cancer progression; (2) to correlate expression of adhesion molecules with grade of tumour differentiation; and (3) to correlate clinicopathological variables with lymph node metastasis and depth of tumour invasion.

Patients and methods

Tumour specimens

Formalin-fixed, paraffin-embedded gastric carcinoma tissue samples were obtained from the archival tissue bank of the pathology department at Saga Medical School. Specimens were obtained from a total of 143 consecutive patients with early gastric carcinoma: 47 intramucosal carcinomas (1989–1991) and 96 submucosal carcinomas (1989–1997). All patients had undergone gastrectomy. The specimens were examined macroscopically and histologically based on criteria proposed by the Japanese Research Society for Gastric Cancer[2]. In addition, tumours were divided into two histological groups according to the Japanese Classification of Gastric Carcinoma[2]: (1) differentiated-type cancer, which consisted of papillary adenocarcinoma and well and moderately differentiated adenocarcinoma, and (2) undifferentiated-type cancer, which consisted of solid and non-solid poorly differentiated adenocarcinoma and signet-ring cell carcinoma.

A section from each specimen block was stained with haematoxylin and eosin for histological evaluation, and representative blocks were used for immunohistochemical studies. In addition, normal gastric mucosa adjacent to the tumour was used as an internal control for normal membranous staining of E-cadherin and α- and β-catenin.

Monoclonal antibodies

Mouse monoclonal immunoglobulin G (IgG) antibodies against human E-cadherin and α- and β- catenin (Transduction Laboratories, Lexington, Kentucky, USA) were used. Appropriate antibody dilutions were determined by serial titration in the presence of positive and negative controls. Final dilutions were as follows: anti-E-cadherin 1 : 50, anti-α-catenin 1 : 200 and anti-β-catenin 1 : 100.

Immunohistochemistry

Formalin-fixed, paraffin-embedded tissue blocks were cut into sections 4 μm thick for haematoxylin and eosin staining and immunohistochemistry. Sections were dewaxed using xylene and transferred to alcohol. Antigen retrieval was performed by microwave for 15 min in citric buffer (citric acid monohydrate 10 mmol/l, pH 6·0). Endogenous peroxidase was blocked by immersion in 3 per cent hydrogen peroxide for 10 min at room temperature. To reduce non-specific background staining, 10 per cent normal goat serum was placed on the sections for 10 min at room temperature. After washing in phosphate-buffered saline (PBS), the sections were incubated overnight with the primary antibody (in PBS containing 1 per cent bovine serum albumin) at 4°C in a humidified chamber. The sections were washed in PBS and incubated with goat antimouse IgG conjugated to peroxidase-labelled dextran polymer (DAKO Envision+™; DAKO, Carpinteria, California, USA) for 30 min. After further washing in PBS, the sections were developed with activated 3,3-diaminobenzidine tetrahydrochloride solution for 5 min, and the reaction was stopped in water. The sections were then counterstained with haematoxylin and dehydrated in alcohol before mounting. As a negative control, primary antibody was replaced with mouse IgG. In addition to using adjacent non-involved gastric mucosa as an internal positive control, positive controls using normal gastric mucosa were used with each batch.

Immunohistochemical findings were scored independently by three observers (G.E., Y.K. and M.T.) who were blinded to the clinicopathological details. A high level of concordance was achieved among the raters; any discrepancies were resolved by consensus. The expression of E-cadherin and α- and β-catenin in malignant cells was compared with that of normal epithelial cells. The staining pattern was classified into four groups[14]. Only a membranous pattern, which stained as strongly as normal epithelial cells, was judged as normal. In contrast, absent pattern (loss of staining), cytoplasmic pattern (cytoplasmic staining with loss of membranous expression) and heterogeneous pattern (cytoplasmic staining with preservation of membranous expression) were considered abnormal. Only β-catenin showed additional nuclear staining, which was judged as abnormal. In the case of mixed patterns in some sections, the classification was determined by the most dominant pattern.

Statistical analysis

Statistical analysis was performed by the χ^2 test. Student's *t* test was used to determine group differences. Univariate and multivariate analyses (logistic regression model) were used to examine the relationships between submucosal invasion of the tumour and lymph node metastasis, and various risk factors. For all statistical analysis, StatView 5.0 software (SAS Institute, Cary, North Carolina, USA) was used. $P < 0{\cdot}05$ was considered statistically significant.

Results

A total of 143 early gastric cancers was examined for E-cadherin and α- and β-catenin. Four patterns of E-cadherin immunostaining are shown in *Fig. 1a–d*. Normal E-cadherin and α- and β-catenin staining was observed in 31, 38 and 31 per cent respectively of tumours examined. Only β-catenin showed additional nuclear staining that was considered abnormal (*Fig. 1e*).

Relationship with clinicopathological features

The relationships between immunostaining and clinicopathological characteristics of all 143 patients are shown in *Table 1*. Gender, age and tumour size showed no correlation with either E-cadherin or the two catenins. The depth of wall invasion was significantly correlated with E-cadherin and β-catenin staining. Abnormal expression of E-cadherin and β-catenin was increased in submucosal cancer compared with intramucosal cancer (both $P < 0{\cdot}01$). Histological tumour type was significantly correlated with immunostaining of E-cadherin and α- and β-catenin ($P < 0{\cdot}05$, $P = 0{\cdot}01$ and $P < 0{\cdot}01$ respectively). The frequency of abnormal E-cadherin and α- and β-catenin staining was lower in differentiated-type tumours (64, 51 and 55 per cent respectively) than in undifferentiated-type tumours (80, 79 and 76 per cent respectively). Lymphatic vessel invasion was also correlated with immunostaining of E-cadherin and β-catenin. Lymph node metastasis was correlated significantly only with β-catenin staining ($P = 0{\cdot}02$). Lymph node metastasis was observed in only two (5 per cent) of 45 patients with normal β-catenin staining but in 19 (19 per cent) of 98 patients with abnormal β-catenin staining.

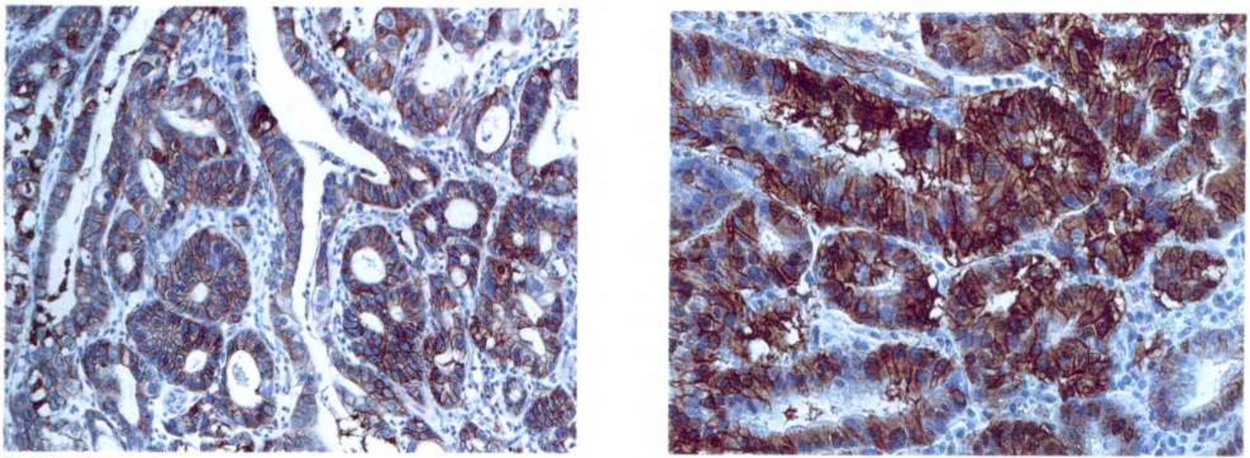
Relationship with depth of wall invasion

Because abnormal expression of E-cadherin and β-catenin increased with the progression of early gastric carcinoma (*Table 1*), the relationship between the depth of wall invasion and expression of E-cadherin–catenin complex was assessed in each histological tumour type (*Table 2*).

In differentiated-type carcinoma, E-cadherin and β-catenin staining correlated with the depth of wall invasion (both $P < 0{\cdot}01$). Abnormal E-cadherin and β-catenin staining was observed in 12 (33 per cent) and 11 (31 per cent) of 36 intramucosal carcinomas, and in 50 (82 per cent) and 38 (62 per cent) of 61 submucosal carcinomas respectively. In contrast, in undifferentiated-type carcinoma, abnormal staining of E-cadherin and β-catenin was observed in nine (82 per cent) of 11 intramucosal carcinomas and in 28 (80 per cent) and 32 (91 per cent) of 35 submucosal carcinomas respectively. Abnormalities in E-cadherin and β-catenin staining were nearly identical between intramucosal and submucosal carcinomas in undifferentiated-type cancer. However, no significant correlation was observed between abnormal α-catenin staining and the depth of wall invasion in either histological tumour type.

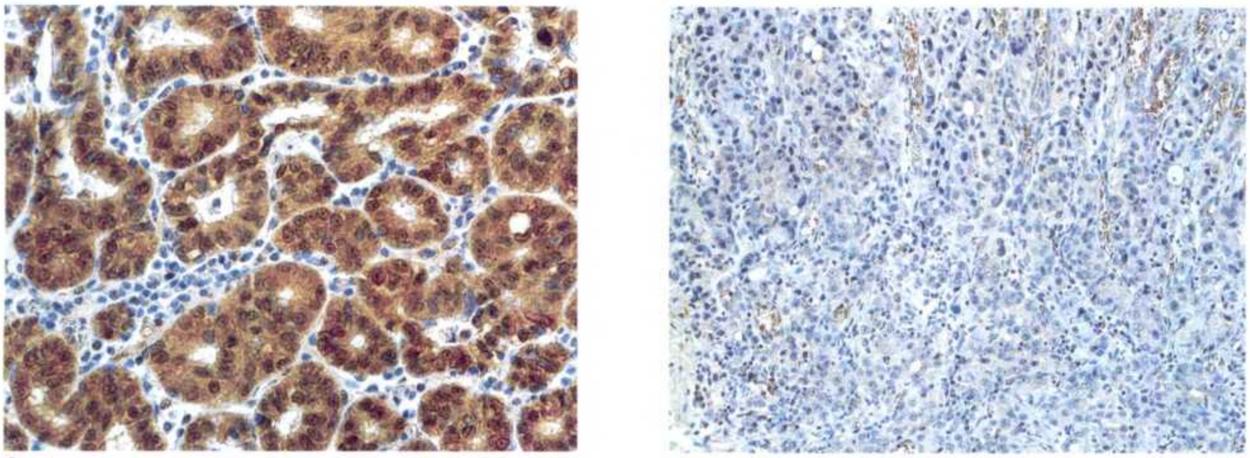
Comparison of immunostaining patterns

Qualitative differences in abnormal expression of the adhesion molecules between the two histological tumour types were assessed by comparing staining patterns of E-cadherin and α- and β-catenin in the 143 early gastric carcinomas (*Fig. 2*). An absent staining pattern was observed predominantly in undifferentiated-type tumours (67 per cent for E-cadherin and α-catenin, and 78 per cent for β-catenin), while normal membranous staining was most frequently found in differentiated-type tumours



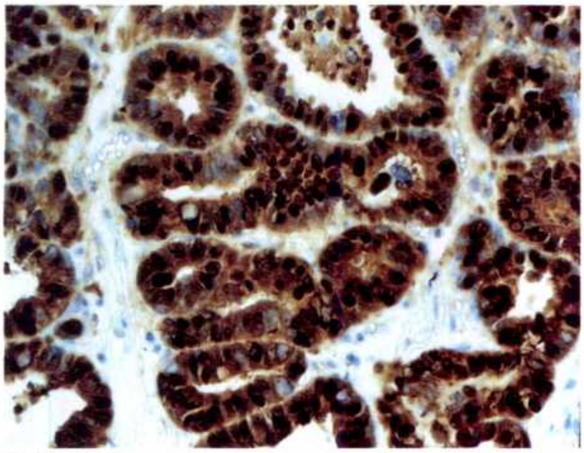
a Membranous

b Heterogeneous



c Cytoplasmic

d Absent



e Nuclear

Fig. 1 Representative immunohistochemical staining for E-cadherin and α- and β-catenin in early gastric carcinoma. **a** membranous pattern: well differentiated adenocarcinoma with normal membranous E-cadherin immunostaining (original magnification × 200). **b** Heterogeneous pattern: moderately differentiated adenocarcinoma showing both membranous and cytoplasmic E-cadherin staining (original magnification × 400). **c** Cytoplasmic pattern: moderately differentiated adenocarcinoma showing cytoplasmic distribution of E-cadherin staining (original magnification × 400). **d** Absent pattern: poorly differentiated adenocarcinoma showing loss of E-cadherin staining (original magnification × 400). **e** Nuclear pattern: moderately differentiated adenocarcinoma showing nuclear staining pattern with or without membranous or cytoplasmic distribution of β-catenin (original magnification × 400)

Table 1 Relationship between clinicopathological features and immunohistochemistry

	E-cadherin			β-Catenin			α-Catenin		
	Normal	Abnormal	*P*†	Normal	Abnormal	*P*†	Normal	Abnormal	*P*†
Gender			0·55			0·06			0·41
Male	28	68		36	60		36	60	
Female	16	31		9	38		19	28	
Age (years)*	62·0(13·1)	63·1(11·1)	0·60	61·4(12·0)	63·3(11·6)	0·35	63·7(11·5)	62·1(11·8)	0·42
Size (cm)*	2·31(1·59)	2·47(1·47)	0·57	2·24(1·32)	2·50(1·58)	0·36	2·35(1·52)	2·46(1·50)	0·65
Tumour type			< 0·01			< 0·01			0·97
Mucosal	26	21		23	24		18	29	
Submucosal	18	78		22	74		37	59	
Histological type			< 0·05			< 0·01			0·01
Differentiated	35	62		41	56		44	53	
Undifferentiated	9	37		4	42		11	35	
Node status			0·45			0·02			0·31
Positive	5	16		2	19		6	15	
Negative	39	83		43	79		49	73	
Lymphatic invasion			< 0·01			0·04			0·42
Positive	3	28		6	26		10	21	
Negative	41	71		40	72		45	67	
Venous invasion			0·07			0·66			0·80
Positive	0	7		2	5		3	4	
Negative	44	92		43	93		52	84	
Stage			0·31			0·09			0·46
Ia	41	83		43	81		50	74	
Ib	2	11		2	11		3	10	
II	1	5		0	6		2	4	

*Values are mean(s.d.). †Student's *t* test for differences in age and size; otherwise χ^2 test

(36 per cent for E-cadherin, 49 per cent for α-catenin and 45 per cent for β-catenin). Lower rates of heterogeneous, cytoplasmic and absent patterns were found in the differentiated-type tumours.

Relationship with lymph node metastasis

Lymph node metastasis in early gastric cancer was clinicopathologically related with the depth of tumour invasion ($P < 0.05$), histological type ($P < 0.05$), lymphatic vessel invasion ($P < 0.01$) and tumour stage ($P < 0.01$). Immunohistochemical analysis of the adhesion molecules indicated that β-catenin expression correlated with lymph node metastasis ($P < 0.01$). Specifically, lymph node metastasis was more common in tumours that showed an absent staining pattern for β-catenin (16 of 56; 29 per cent) than normal staining tumours (two of 45; 4 per cent) (*Table 3*).

Factors related to lymph node metastasis and depth of wall invasion

Univariate analysis showed a correlation between β-catenin expression and lymph node metastasis. Multivariate analysis using the logistic regression model was then performed to identify which of the factors significantly influenced lymph node metastasis. Only lymph vessel invasion was independently correlated with lymph node metastasis in early gastric cancer (data not shown).

The same process was used to identify independent predictors of submucosal tumour invasion. Univariate analysis identified a significant correlation between tumour size, lymphatic invasion, E-cadherin and β-catenin expression, and submucosal invasion. Multivariate analysis using the logistic regression model demonstrated that only tumour size and E-cadherin expression were independent predictors of submucosal invasion in differentiated-type early gastric cancer (*Table 4*).

Staining intensity

In the majority of tumours, the same intensity of each staining pattern was observed between the mucosal and submucosal portions. Furthermore, the staining patterns remained the same for most tumours that expressed increased or decreased intensity of staining in the submucosal portion.

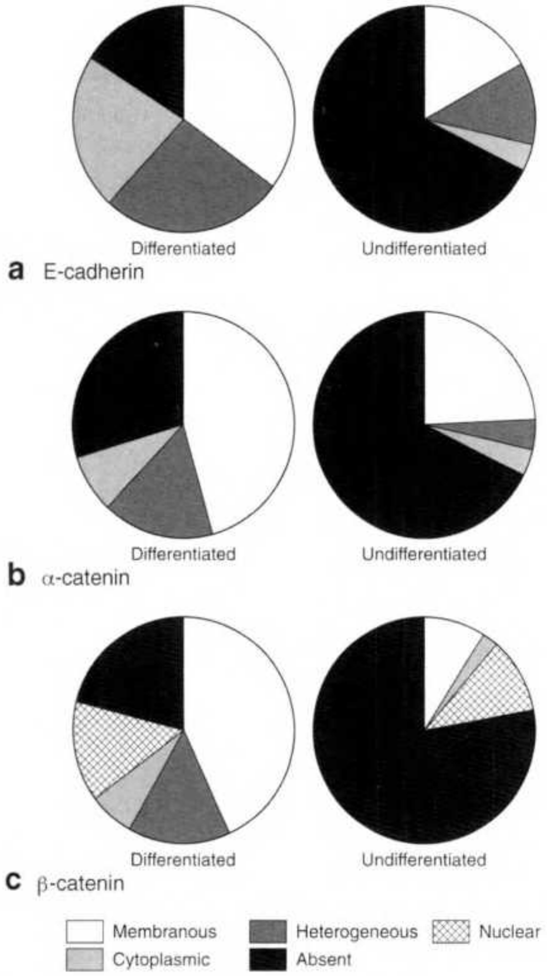


Fig. 2 Comparative study of E-cadherin and α- and β-catenin staining patterns between two histological tumour types in 143 cases of early gastric carcinoma

Discussion

The pathogenesis of gastric cancer remains largely unknown. Although a number of genetic or molecular alterations have been described in gastric carcinoma, their exact sequence has yet to be established[29]. Tahara *et al.*[30] reported that accumulated alterations in structure and function of oncogenes and tumour suppressor genes are responsible for carcinogenesis, invasion and metastasis of gastric cancer. They further indicated that different genetic pathways may exist for intestinal- and diffuse-type gastric cancers[30,31].

Pathological studies have also indicated that atrophic gastritis and intestinal metaplasia represent important intermediate steps in the pathogenesis of intestinal-type gastric cancer[32]. On the other hand, such precancerous lesions are not found in diffuse-type carcinoma[31]. These previous reports suggest different pathways for carcinogenesis and cancer progression in the two types of gastric carcinoma. The first step leading to invasion and metastasis is assumed to be cancer cell detachment, which requires modulation of cell–cell interactions. Thus, early gastric cancer is proposed to be a suitable model for investigating carcinogenesis or early events in cancer invasion caused by adhesion complex abnormalities, since cancer infiltration is still limited to the mucosa or submucosa.

Immunohistochemical studies using surgically resected specimens have shown abnormal expression of the complex in 30–75 per cent of gastric cancers[11,14,25,33,34]. Jawhari *et al.*[14] have reported that abnormal E-cadherin and γ-catenin staining occurred more frequently in diffuse-type than intestinal-type gastric cancer. Other studies of human gastric cancer have shown relationships between E-cadherin and α- and β-catenin expression and clinicopathological features such as tumour differentiation, prognosis and lymph node metastasis[11–17,35].

Several studies have focused on the expression of these molecules in early gastric cancer[19,25,34]. However, previous

Table 2 Relationship between the depth of wall invasion and immunohistochemical findings

	E-cadherin			β-Catenin			α-Catenin		
Tumour type	Normal	Abnormal	*P**	Normal	Abnormal	*P**	Normal	Abnormal	*P**
Differentiated									
Mucosal	24 (67)	12 (33)	< 0·01	25 (69)	11 (31)	< 0·01	17 (47)	19 (53)	0·77
Submucosal	11 (18)	50 (82)		23 (38)	38 (62)		27 (44)	34 (56)	
Undifferentiated									
Mucosal	2 (18)	9 (82)	> 0·99	2 (18)	9 (82)	0·37	1 (9)	10 (91)	0·18
Submucosal	7 (20)	28 (80)		3 (9)	32 (91)		10 (29)	25 (71)	

Values in parentheses are percentages. *χ^2 test

Table 3 Relationship between β-catenin staining patterns and lymph node metastasis

		Normal	Abnormal			
	Total	Membranous	Heterogeneous	Cytoplasmic	Nuclear	Absent
Lymph node metastasis						
Positive	21 (15)	2 (4)	1 (7)	1 (13)	1 (5)	16 (29)*
Negative	122 (85)	43 (96)	14 (93)	7 (87)	18 (95)	40 (71)

Values in parentheses are percentages. $^*P < 0·01$ *versus* normal (χ^2 test)

Table 4 Factors related to depth of wall invasion

	Univariate analysis		Multivariate analysis	
Independent factors	Relative risk	*P*	Relative risk	*P*
Tumour size	1·79 (1·22, 2·64)	< 0·01	1·57 (1·00, 2·56)	< 0·05
Lymphatic vessel invasion (positive *versus* negative)	14·72 (0·01, 0·54)	0·01	3·14 (0·04, 2·92)	0·31
Lymph node metastasis (positive *versus* negative)	6·06 (0·02, 1·36)	0·09	4·13 (0·02, 2·67)	0·25
β-Catenin expression (normal *versus* abnormal)	3·76 (1·56, 9·04)	< 0·01	1·96 (0·68, 5·70)	0·22
E-cadherin expression (normal *versus* abnormal)	9·09 (3·51, 23·50)	< 0·01	7·25 (2·45, 21·40)	< 0·01

Values in parentheses are 95 per cent confidence intervals. Logistic regression model was used for multivariate analyses between various risk factors

assessments of E-cadherin–catenin complex immunoreactivity in early gastric cancer were based on comparisons with staining intensity of normal gastric epithelium and, in general, these studies combined intramucosal and submucosal carcinomas. The present study investigated immunostaining patterns as well as abnormal expression of the adhesion complex at distinct stages (intramucosal and submucosal carcinoma). The authors postulated that loss of normal membranous staining of any component of the cadherin–catenin complex would disrupt its function and contribute to the malignant phenotype.

Abnormalities of E-cadherin and β-catenin staining in the differentiated-type cancer did not increase until the submucosal carcinoma stage, whereas the abnormalities were frequently found at the intramucosal carcinoma stage in undifferentiated-type cancer. These results strongly suggest that abnormal E-cadherin and β-catenin expression contributes to carcinogenesis of gastric cancer or early-phase progression in undifferentiated-type carcinoma. In contrast, abnormalities in E-cadherin and β-catenin probably occur at a later phase in the progression of gastric cancer in differentiated-type carcinoma. Furthermore, heterogeneous and cytoplasmic patterns in adhesion molecules were found in differentiated-type carcinoma, whereas absent immunostaining of E-cadherin and α- and β-catenin was observed predominantly in undifferentiated-type cancer. This sharp contrast between the two cancer types indicates that different alterations in adhesion molecule genes may occur in differentiated and undifferentiated cancers.

Preoperative assessment of invasion depth as well as lymph node metastasis is critical for determining appropriate therapies for early gastric cancer. Endoscopic ultrasonography is widely used for preoperative estimation of invasion depth, whereas conventional studies, including ultrasonography and computed tomography (CT), are used for preoperative assessment of lymph node metastases. However, endoscopic ultrasonography does not distinguish sufficiently between mucosal and submucosal cancer, and ultrasonography or CT does not satisfactorily detect small lymph node metastases. Therefore, biomarkers that predict submucosal tumour infiltration as well as lymph node metastasis may allow surgeons to select the most appropriate initial treatment.

Multivariate analysis of factors related to invasion depth identified E-cadherin expression as an independent predictor of submucosal invasion in only differentiated-type early gastric cancer. Conventional clinicopathological factors, such as tumour staging and lymphatic vessel invasion, have been reported to correlate with lymph node metastasis. However, they could not be used for predicting lymph node metastasis before surgery. Xiangming *et al.*[25,34] reported that a combination of reduced α-catenin expression and overexpression of p53 can be used to predict lymph node metastasis in early gastric cancer. In the present study, multivariate analysis did not demonstrate that abnormal β-catenin is an independent predictor of lymph node metastasis, although univariate analysis showed a significant correlation between abnormal β-catenin and lymph node metastasis in early gastric cancer. In particular, absent β-catenin immunostaining was a significant indicator of increased lymph node metastasis.

The present comparative study of E-cadherin and β-catenin immunostaining between the mucosa and submucosa in 96 submucosal cancers revealed that most tumours exhibited homogeneous staining intensity and the same patterns between the mucosal and submucosal layers. Therefore, biopsy specimens obtained before operation could be used to predict tumour depth and lymph node metastasis by E-cadherin and β-catenin expression respectively. This preoperative estimation may allow selection of minimally invasive treatment, such as endoscopic mucosal resection or limited surgery, for early gastric cancer.

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Correspondence

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Saphenoperitoneal shunts for patients with intractable ascites associated with chronic liver disease (*Br J Surg* 1999; 86: 882–5)

Sir

We found this article not only very interesting but useful, and have tried it with limited success in Michigan. We were easily able to perform the dissection with a slight modification, using two parallel oblique incisions on the anterior abdomen and thigh rather than one long L-shaped incision. This saved our malnourished patient (as so many cirrhotic patients are) the morbidity of a lengthy incision and allowed her to heal more quickly. We did not complete the procedure successfully due to the fact that we did not adequately spatulate the saphenous vein prior to anastomosis. We were, however, able to salvage the procedure using the saphenous vein and internal inguinal ring as access points for a LeVeen shunt, which worked well.

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Microcirculatory effects of experimental acute limb ischaemia–reperfusion (*Br J Surg* 2001; 88: 816–24)

Letter 1

Sir

Although this study was well conducted, I believe the conclusion that this represents a new model to study the pathophysiological mechanisms of limb ischaemia–reperfusion (I-R) must be treated with caution. The model is a further adaptation of one described by Rosenthal and Thornton[1]. In the assessment of reperfusion injury the use of intravital video microsopy is also well established both in tissues[2] and skin[3] of rats. The main concerns, however, relate to the effects of tourniquet ischaemia and subsequent interpretation of skin leucocyte–vessel wall interactions in the ipsilateral limb, which has been subjected to both combined arterial and venous obstruction and crush injury (cuff pressure 300 mmHg). We have previously shown that concomitant venous obstruction compounds local and remote hind limb I-R injury[4] in a non-tourniquet model. It cannot be assumed that venous congestion and crush injury do not influence skin leucocyte–vessel wall interaction, making any conclusions drawn on what is essentially an artificial mechanism of injury invalid. We find it unusual that no evidence of no-reflow and reflow-associated events, including leucocyte–endothelium interaction and increase in microvascular permeability, has been reported, especially since none of the experimental animals appear to have been given heparin. No-reflow is surely compounded by capillary closure, venous obstruction and tissue trauma from the tourniquet-induced ischaemia?

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Letter 2

Sir

I would like to draw your attention to the anaesthetic protocol described by the authors. Rats were subjected to a 'short sedation by carbon dioxide (40 per cent carbon dioxide in air)' prior to inducing anaesthesia by the intraperitoneal administration of sodium pentobarbital. I must question the suitability and appropriateness of using carbon dioxide in this setting on the following grounds. First, inhalation of 40 per cent carbon dioxide in air results in hypoxia and hypercapnia (and consequently acidosis). What influence would these changes have on the response to the ischaemia subsequently produced? Second, the appropriateness of 40 per cent carbon dioxide in air must also be questioned. A level of 60 per cent (or above) is required to produce anaesthesia in rats and it is known that inhalation of 40 per cent carbon dioxide actually causes excitation. Use of carbon dioxide in air, without admixture of oxygen, causes pronounced dyspnoea[1]. In addition, studies in a range of species have conclusively demonstrated the aversive properties of carbon dioxide when inhaled[2,3].

In light of the above I must question whether the authors were justified, from both the scientific and welfare viewpoints, in using carbon dioxide as a sedative.

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1 Kohler I, Meier R, Busato A, Neiger-Aeschbacher G, Schatzmann U. Is carbon dioxide a useful short acting anaesthetic for small laboratory animals? *Lab Anim* 1999; **33:** 155–61.
2 Cooper J, Mason G, Raj M. Determination of the aversion of farmed mink (*Mustela vison*) to carbon dioxide. *Vet Rec* 1998; **143:** 359–61.
3 Raj AB. Behaviour of pigs exposed to mixtures of gases and the time required to stun and kill them: welfare implications. *Vet Rec* 1999; **144:** 165–8.

Prospective study of primary anastomosis following sigmoid resection for suspected acute complicated diverticular disease (*Br J Surg* 2001; 88: 693–7)

Sir

I would like to comment on a few aspects of this interesting paper. First, I congratulate the authors for their commendably low mortality rate. It would be nice to know the actual number of exclusions, as this series mentions 45 consecutive patients in five large teaching hospitals who underwent resection and anastomosis over a 2-year period. How many Hartmann's procedures were carried out in this period of time in these hospitals? Were any preoperative investigations (i.e. contrast enemas or computed tomography scans) employed or was the decision to operate based purely on clinical deterioration? Peroperative lavage was carried out in only eight patients and one wonders whether any particular protocol was followed in its application? Eleven per cent of patients had carcinoma identified on histological examination; was an oncological clearance carried out in these cases and were the histological findings favourable? Two of the patients underwent second-look laparotomy as a planned procedure and readers may wish to know the indications. There is a wide difference in the numbers of patients with colonic obstruction ($n = 8$) and abscess/perforation ($n = 37$), and so subgroup analysis may not be clinically significant. A recent report by Watson *et al.*[1] concluded that there was a higher chance of saving the anastomosis, with no mortality, if a leak was detected early and appropriate intervention instituted. How were leaks detected in this series and was intervention carried out early?

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1 Watson AJM, Krukowski ZH, Munro A. Salvage of large bowel anastomotic leaks. *Br J Surg* 1999; **86:** 499–500.

Authors' reply

Sir

This is a consecutive series and only patients with the exclusion criteria described (previous irradiation of pelvic organs and faecal incontinence) were excluded and a Hartmann's procedure performed. The decision to operate was based on clinical deterioration or acute development of severe illness with left lower quadrant abdominal pain suggestive of local or diffuse peritonitis due to complicated diverticular disease.

As all patients were operated on in the emergency situation bowel preparation was not carried out. Peroperative lavage was not part of our protocol and was not performed in any of the cases. Patients who were found to have a carcinoma on histological examination had the same operation as the others, since acute complicated diverticular disease was the indication for surgery. We do not report histological findings because it falls beyond the scope of this study.

The planned second-look procedure was carried out according to indications set by the responsible surgeon. Both patients had grade II–III purulent and faecal peritonitis. There is, indeed, a wide difference in numbers of patients with colonic obstruction and abscess/perforation. It might represent two different categories of patients. Anastomotic leakage was detected by clinical deterioration or drainage of faecal material through drains, wounds or fistulas and by formation of intra-abdominal fluid collections. Intervention was carried out as an emergency following detection.

The treatment of patients with acute complicated diverticular disease remains a subject of continuing debate in general surgical practice. The question of whether primary or secondary anastomosis should be conducted will hopefully be answered by the randomized trial comparing Hartmann's procedure with primary anastomosis without protection currently being carried out in the Netherlands (multicentre trial). There is definitely a need for stratification of patients into groups, separating those with relatively mild disease from septic patients who are likely to develop a severe systemic response. At present we must avoid any message suggesting that severely septic patients do well with primary anastomosis in inexperienced hands.

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Use of minilaparotomy in the treatment of colonic cancer (*Br J Surg* 2001; 88: 831–6)

Letter 1

Sir

Five of the 84 patients could not undergo resection by minilaparotomy because of local tumour invasion and one patient had a large tumour that could not be removed through the smaller incision. Is there a role for preoperative staging laparoscopy to assess tumour fixity and size? Minilaparotomy is as effective as laparoscopic surgery in reducing postoperative hospital stay[1]. In this context, is there a role for minilaparotomy in patients with metastatic colorectal cancer who need palliative resection?

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1 Fleshman JW, Fry RD, Birnbaum EH, Kodner IJ. Laparoscopic-assisted and minilaparotomy approaches to colorectal diseases are similar in early outcome. *Dis Colon Rectum* 1996; **39**: 15–22.

Letter 2

Sir

We would like to know how tumour size was assessed preoperatively. We presume that tumours more than 6 cm in size could not be delivered through a 7-cm incision without contamination and the risk of port-site recurrence.

Despite the availability of spiral computed tomography and magnetic resonance imaging for assessment of liver involvement[1], we believe that intraoperative assessment by inspection and palpation combined with intraoperative ultrasonography[2,3] is essential. How did the authors evaluate the liver through a minilaparotomy incision?

The authors performed ten ileocaecal resections as opposed to right hemicolectomy. Do they consider ileocaecal resection sufficient when right hemicolectomy will afford a greater likelihood of lymphatic clearance?

An added advantage of laparoscopic mobilization is the ability to mobilize the splenic flexure. If the authors combined laparoscopy to assist left colonic resection via a minilaparotomy, we believe they may have avoided conventional open procedures in five patients in whom they encountered difficulty with mobilization of the flexure because of access through a minilaparotomy.

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1 Zerhouni EA, Rutter C, Hamilton SR, Balfe DM, Megibow AJ, Francis IR *et al.* CT and MR imaging in the staging of colorectal carcinoma: report of the Radiology Diagnostic Oncology Group II. *Radiology* 1996; **200**: 443–51.
2 Kolecki R, Schrimer B. Intraoperative and laparoscopic ultrasound. *Surg Clin North Am* 1998; **78**: 251–71.
3 Foley EF, Kolecki RV, Schirmer BD. The accuracy of laparoscopic ultrasound in the detection of colorectal cancer liver metastases. *Am J Surg* 1998; **176**: 262–4.

Author's reply

Sir

In reply to the letter from Mr Somasekar, we believe that preoperative staging laparoscopy is unnecessary because, in general, tumours invading adjacent organs or large tumours should be resectable. Preoperative staging laparoscopy does not therefore change the operative procedure, but the minilaparotomy may have to be abandoned. Preoperative staging laparoscopy does require general anaesthesia. Our procedure involves a 7-cm minilaparotomy to assess local fixity and tumour size. When local fixity and/or a large tumour is found, the incision is elongated. Patients with metastases of the liver, para-aortic lymph nodes or the other distant organs were excluded. As Mr Somasekar mentioned, we believe that the minilaparotomy approach is useful in some patients with metastatic colorectal cancer who need palliative resection. Minilaparotomy may be effective in reducing the postoperative hospital stay and the faster postoperative recovery may allow earlier initiation of adjuvant therapy.

In reply to the letter from Ranatunga *et al.*, we assessed tumour size using routine preoperative computed tomography, although the exact tumour size cannot always be determined by this method. In order to avoid cancer cell contamination of the minilaparotomy wound, a tumour larger than 6 cm should not be delivered via a 7-cm minilaparotomy. In such cases, the incision should be elongated. Incidentally, we routinely use a minilaparotomy edge protector (Lap-Protector®), which we developed recently, to prevent infections and cancer cell contamination of the minilaparotomy wound[1].

In our experimental series, we used computed tomography and ultrasonography (magnetic resonance imaging when necessary) for preoperative assessment of liver involvement, and we did not perform intraoperative assessment for liver metastasis. As Fleshman *et al.*[2] have proposed, patients in whom full visualization of the abdomen is required may be best suited to laparoscopy. Use of laparoscopic view and ultrasonography can facilitate intraoperative assessment of liver involvement in these patients. Removal of lymph nodes along the ileocolic artery and at the root of the ileocolic artery is a necessary and sufficient procedure for the cure of caecal cancer[3]. Therefore, we believe that right hemicolectomy, which requires removal of lymph nodes along both the right colic artery and the right branch of the middle colic artery, as well as along the ileocolic artery, is unnecessary for patients with caecal cancer. Recently, we have performed mobilization of the splenic flexure by means of gasless, hand-assisted laparoscopic surgery[4] using the original 7-cm laparotomy incision for patients with colonic cancer in whom mobilization of the splenic flexure was required. We believe that a combination of laparoscopy and minilaparotomy techniques is useful for such patients.

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1 Nakagoe T, Sawai T, Tsuji T, Nanashima A, Jibiki M, Yamaguchi H *et al.* Minilaparotomy wound protector (Lap-Protector): a new device. *Surg Today* 2001; **31:** 850–2.
2 Fleshman JW, Fry RD, Birnbaum EH, Kodner IJ. Laparoscopic-assisted and minilaparotomy approaches to colorectal diseases are similar in early outcome. *Dis Colon Rectum* 1996; **39:** 15–22.
3 Japanese Society for Cancer of the Colon and Rectum. *Japanese Classification of Colorectal Carcinoma. 1st English ed.* Tokyo: Kanehara, 1997.
4 Miura Y, Mitsuta H, Yoshihara T, Ohshiro Y, Okajima M, Asahara T *et al.* Gasless hand-assisted laparoscopic surgery for colorectal cancer: an option for poor cardiopulmonary reserve. *Dis Colon Rectum* 2001; **44:** 896–8.

Intestinal Failure

J. Nightingale (ed.)

250 × 190 mm. Pp. 565 2001 London Greenwich Medical Media £85 00

As recently as 30 years ago the 'pioneers' Dudrick, Wilmore, Vars and Rhoads developed the cornerstone concept of parenteral nutrition. Since the introduction of this compensatory mechanism to clinical practice, cachexia due to reduced intestinal absorption is a thing of the past; this has been a formidable step in gastroenterological and surgical sciences. The concept of intestinal failure is relatively new and not yet part of core medical teaching, as in the case of other organ impairments. As a consequence, the title of this book appears to be original and stimulating. An international team of clinicians, dieticians, nurses and pharmacists has, in eight sections and 34 chapters, discussed topics from an introductory chapter of historical overview, to definitions, causes, management, consequences and outcome of acute and chronic intestinal failure. The final result is a comprehensive book; reading several chapters one becomes aware that each writer describes events that occur in clinical practice every day, resulting in a practical guide. Clearly written with up-to-date references, the book is well produced. Particularly useful are the appendices and the list of useful websites (good idea) dealing with enteral and parenteral nutritional problems. I shall recommend this book to my residents in surgery and gastroenterology.

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Complications in Vascular and Endovascular Surgery, Part 1

A. Branchereau and M. Jacobs (eds)

277 × 215 mm Pp 283 Illustrated 2001 New York Futura $125 00

The foreword in this book tells us that it is based on the European Vascular Course 2001, but does not give any information regarding the course. This volume is Part 1 of a two-part book devoted to the complications of vascular and endovascular surgery. Part 1 has 29 contributions from 95 (mostly European) authors on a variety of complications encountered in vascular practice. The scope of the volume is quite wide and includes chapters about carotid, renal, thoracic–aortic and venous surgery among others. The book contains a lot of information but it is not clear at whom it is aimed. Chapters vary from those that address basic concepts, such as healing and adaptation of grafts in the arterial circulation, to clinical chapters that give advice on the management of specific complications, such as contrast-induced renal failure and graft infection. There is almost nothing about reperfusion injury. I suspect that vascular surgeons would be most interested in an overview of the management of the complications of aortic and lower limb vascular surgery (including endovascular surgery), but they will have to wait until Part 2 for this. This volume is nicely produced but is a little short on illustrations; most irritatingly, it has no index. The management of complications after vascular and endovascular surgery is challenging, but this book is not focused enough to be an essential text for practising vascular surgeons who have to deal with these difficult problems.

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Vascular and Endovascular Surgery. 2nd Ed.

J. D. Beard and P. A. Gaines (eds)

250 × 190 mm Pp 546. Illustrated 2001. London WB Saunders £59·95.

The second edition of this concise and readable textbook is intended to meet 'the needs of higher surgical trainees and busy practising surgeons'. It has been updated with recent references, many from within the last 18 months. Despite having multiple contributors, the succinct style and clear format, with key paragraphs clearly marked, provides a readable text throughout. The contributors are all authorities in their topics and summarize their wide knowledge within the unified style. Most chapters include over 100 references. I found the book informative, up to date and readable, and in my view it would be ideal for informing surgical trainees and surgeons of recent developments and practice.

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Minor Surgery: A Text and Atlas. 4th Ed.

J. S. Brown

276 × 207 mm Pp 470 Illustrated 2000 London. Arnold £85 00

The majority of this book is written by one author, the exceptions being a few specialist sections at the end. This provides a consistent style and standardization of approach that makes the volume extremely user-friendly. It is clear, comprehensive and very well illustrated. All of this makes it a valuable reference for general practitioners and surgeons whether they are in training and or a more senior post. Only minor criticisms can be applied. For example, in such a publication, do we need a copy of the author's specimen operating list or a statistical analysis of 5 years of his personal practice? The preface to the first edition states that the author's aim was to provide a valuable reference book on minor surgery. That it is now in its fourth edition, 15 years later, is a testament to the author and proof of success of this aim. Even though there are other well known books on similar themes, the topical subject matter covered here will ensure this volume's continued success.

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Stell and Maran's Head and Neck Surgery. 4th Ed.

J. C. Watkinson, M. N. Gaze and J. A. Wilson
282 × 202 mm. Pp. 520. Illustrated. 2000. London: Arnold. £85·00.

This book is primarily written by the three authors above, but three additional authors have written specific chapters. It is well written, although possibly a little didactic for the present age, and I understand that this may well have been a specific aim of the authors, following the example of Professors Stell and Maran, but I do not feel it is entirely appropriate. The book is very well produced and I particularly liked the summary boxes in a different colour; it is reasonably well illustrated. Although the reference section in each chapter is patchy (one chapter having only one reference), referencing generally is adequate. Those with knowledge of the literature of head and neck problems will see that there are numerous prominent and salient publications that have not been included. This suggests to me that the authors are merely quoting those references that they adhere to. To some extent we all do this, and one certainly needs to provide references supporting what has been stated in the chapter. Nevertheless, I would like to have seen a more exhaustive reference section as this would have made the volume more useful to senior head and neck surgeons, although I appreciate the book might not have been aimed at this particular group of individuals.

Chapter 1, 'The nature of head and neck cancer', is nowhere near exhaustive enough and gives a skewed impression of this crucially important topic. Here, in particular, the referencing is poor with a large number of essential references omitted. Chapter 4, 'Treatment options: the principles of surgery', is not entirely successful but it is a difficult topic on which to write. In contrast, chapter 5, 'Principles of nonsurgical treatment', is excellent and will be of use to the junior and senior head and neck surgeon alike. Moving on to the chapter on neck dissection, this is good, and I particularly like Table 13·1 where modified radical neck dissection is summarized in its various types. In Table 13·2 the types of selective neck dissection are also described. Classification of neck dissections has been a bugbear of head and neck surgery for many years and I am glad to see a chapter that attempts to clarify the taxonomy but, regrettably, the chapter is flawed by a minute reference section with notable omissions from the reference list. A minor point is that the writer of the introductory quotation that starts each chapter is not attributed. Chapters 14–17 and 19–23, dealing with specific sites in the head and neck, are all good. I would suggest that, nowadays, there are more references available that could have been included in chapter 15, which is about tumours of the oral cavity for maxillofacial head and neck surgeons. Chapter 18 is entitled 'Rehabilitation of speech and swallowing'; rehabilitation of the lower airways should have been included as there is a lot of interest now in attempting to protect the lungs following total laryngectomy. It is well documented that lung function decreases in these patients and there is some evidence that this decrease can be halted by the use of various prosthetic heat–moisture exchange devices.

Generally speaking, this volume is good and it seems to be aimed primarily at the trainee head and neck surgeon, particularly surgical oncologists. I feel it will perform this function very well and I recommend it to trainees with a particular interest in this field.

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Diagnosis and Surgery of Organ Metastases

I. Besznyak (ed.)
243 × 173 mm. Pp. 350. Illustrated. 2000. Budapest: Akadémiai Kiadé. $74·00.

Originating from the National Institute of Oncology in Budapest, Hungary, this book is a very pleasing read for surgeons particularly involved in the management of patients with metastatic malignant disease. It is a comprehensive text dealing with all the contemporary issues such as the optimum management of the patient with metastatic liver disease or with bone secondaries. As the title suggests, each chapter deals authoritatively with diagnosis, assessment and subsequent surgical treatment (and more broadly interventional treatment) of the patient with metastatic disease. The chapters are laid out in a format that is easy to read and comprehend. Of necessity, many of the chapters are illustrated with various scanning images, which range from poor to very high quality. However, in the vast majority of instances the figure legends and the indicative text fully explain the points being made. While the standard of the chapters varies somewhat, from the adequate to the exceptional, a minor omission might be considered to be the lack of emphasis on the role of surgery or interventional techniques in minimizing cancer pain. Finally, the editors should perhaps have given some thought to including a discussion of quality of life provided by cancer surgery directed at metastatic disease. Overall, this is a pleasing text and a useful addition to our library of books for the surgical oncologist.

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Intraoperative Graft Patency Verification in Cardiac and Vascular Surgery

G. D'Ancona, H. L. Karamanoukian, M. Ricci,
T. A. Salerno and J. Bergsland (eds)
235 × 160 mm. Pp 248 Illustrated 2001 New York. Futura. $80 00

An initial review of rheology, followed by a synopsis of electromagnetic and ultrasound flowmeter technology, concludes that 'transit time flowmetry (TTFM)' is the 'method of choice for perioperative blood flow measurement', having replaced Doppler flow technology (my own current preference) in the early 1990s. The following seven chapters detail the experience of a number of authors of the use of TTFM in cardiac surgery, with only occasional reference to peripheral vascular surgery. The repeated references to the importance of anastomotic quality control in cardiac surgery – particularly in off-pump bypass surgery – makes the absence of evidence of correlation between intraoperative flow measurement and graft patency disappointing. The exception is the contribution from Yves Louagie and his Belgian group in chapter 10, who compared intraoperative flow measurement and graft survival. It is scientifically challenging, carefully analysed and succinctly presented. They used the apparently outdated OpDopp Doppler flowmeter, yet no better chapter can be found in the book, undermining the confidence shown by the authors in the apparently superior technology of TTFM. If vascular surgeons were looking for an authoritative and scientific review of flow measurements, I believe this volume would prove a difficult read but would be of interest.

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Surgical Research

W. W. Souba and D. W. Wilmore (eds)
283 × 215 mm Pp. 1460 Illustrated 2001 San Diego, California
Academic Press £166·95

This new publication is intended to fill an important gap on the shelf of the surgical research laboratory. It aims to act as a reference source of surgical research for the academic surgeon, the trainee and the laboratory scientist. It is primarily a place for young investigators to start, particularly those for whom time in the surgical laboratory will be a relatively brief but formative experience.

The editors have brought together nearly 200 authors, whose bibliography represents a 'who's who' of North American academic surgery. With this large faculty the editors have crafted 100 chapters, yet they have brought a uniformity of style and presentation that makes for easy reading. The sequence of the book very much follows that of the experimental method, starting with experimental design, progressing to experimental methods, data, analysis and presentation, and then passing to the more reflective and historical aspects of surgical research before finishing on practical and managerial subjects. The text provides a framework for further study and a knowledge base for communication with scientists in the related disciplines of surgical research. Chapters dealing with common pathways of experimental design, data analysis and presentation are mandatory reading for the research fellow, and thoughtful reminders to the more senior academic surgeon. Molecular biology dominates the section on research methods but the new language of genes, molecules and cell signalling is explained with clarity and clinical relevance. Chapters on statistical measurement and clinical outcomes are particularly appropriate.

There are of course minor criticisms, particularly the lack of colour in the many excellent illustrations. There is a single set of coloured plates which are out of sequence with textural reference. This seems somewhat old fashioned in such a modern textbook. Less than a quarter of the references in the chapters dealing with molecular biology are citations within the last 5 years. Undoubtedly the basic principles are unchanged but, in such a rapidly developing field, it is hard to see how the editors could have done more given the time required for publication.

This is an important text. It is simply a must for every academic surgical department and a useful aid for every surgical trainee embarking on a research project. The time taken to read it is well spent and will be rewarded with time saved exploring blind alleys. The reader will be inspired with the concept that the modern surgeon scientist is ideally positioned to make major scientific contributions and to apply these contributions to the treatment of human disease (page 1275). It was a privilege to review this book and I can highly recommend it.

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Surgical Critical Care

R. Ashford and N. Evans (eds)

230 × 150 mm. Pp. 247. 2001. London: Greenwich Medical Media. £22·50.

This soft-covered, thin, but 'too large for the pocket' volume is edited by Mr Ashford (trauma and orthopaedics) and Dr Evans (anaesthesia), with contributions by two anaesthetists, a cardiologist, an intensivist, a cardiac surgeon, an orthopaedic surgeon and even a general surgeon. The preface suggests that 'the contents...have been based on the MRCS syllabus of the Royal College of Surgeons of England' and that 'whilst the book is principally aimed as a revision guide for those undertaking the MRCS examination, it will also be useful to those working on a surgical ITU'. The book has been cross-referenced to both *Clinical Surgery in General* (The Royal College of Surgeons of England) and *Surgery* (The Medicine Publishing Group), an excellent review series but virtually unknown on my side of the Atlantic. According to the foreword 'the reader will find a wealth of knowledge woven into the flow diagrams, algorithms and bullet-point lists that reinforce the text material'. I agree that some of the diagrams and flowcharts are good, but the rest is chaotic and the text partially dogmatic, inaccurate, obscure and full of clichés. We are told to use 'Hartmann's solution for trauma and colloids in other circumstances' (which other circumstances and why?). We are also told about pulmonary artery monitoring but not how, why and when. We read that 'Baue classified shock...' – which Baue? In the section about 'anaemia and transfusion' we are instructed to 'transfuse as necessary' but never told when it is necessary. In brief, there is no common sense! We are provided with long and occasionally bizarre bullet-point lists; under the treatment of disseminated intravascular coagulopathy we find, for example, endoscopic retrograde cholangiopancreatography. No less bizarre are statements such as 'Anticoagulation is indicated for venous thromboses. Its role is less certain in arterial embolism'. What is also distressing is that some of the information provided is outdated. Under the treatment of acute pancreatitis the bullet-point list includes the following: nasogastric tube (really?), pulmonary artery catheter (why?), total parenteral nutrition (enteral diet?), and antibiotics 'if infection is present' (what about prophylaxis in severe pancreatitis?).

My heart bleeds for the editors, as I cannot find a good word to say about their book. But as my duty is to be objective, I have to conclude that surgeons, who do not learn well from disorganized, laconic and partially outdated telephone-like directories, would not find this book useful. Perhaps anaesthetists will. Was it not Samuel Johnson who said 'it is advantageous to an author that his book should be attacked...'?

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Abdominal Wall Hernias

R. Bendavid, J. Abrahamson, M. E. Arregui,
J. B. Flament and E. H. Phillips (eds)

280 × 215 mm. Pp. 792. Illustrated. 2001. Heidelberg: Springer. £137·50.

This book was a formidable read and not surprisingly so since it is the work of 160 distinguished contributors. The history of hernia surgery is dealt with in the greatest detail and perhaps to an extent that some might not wish to read. The section on anatomy is excellent and the newer anatomical concepts related to laparoscopy are well described and illustrated. There is good material on occult hernias, and tissue factors in hernia causation are well covered. Biomaterials are comprehensively described although some of those dealt with at length (tantalum gauze, silver filigree) are not of contemporary interest. There is an excellent and well illustrated description of local anaesthetic technique for hernia repair. The historical Bassini operation is described at tedious length. The sections on laparoscopic hernia repair are excellent and the anatomical illustrations are good. There is excellent coverage of the management of abdominal wall loss and the difficult after-effects of laparostomy. Likewise, paediatric abdominal hernias and abdominal wall deficit are well covered. The section on sports injuries, read with anticipation, is disappointing. There is a helpful section on the prevention and management of parastomal hernias. The topics of postoperative nerve pain and medicolegal sequelae of hernia surgery are handled well. The book contains all that is of current interest but also much that (while interesting and important) is historical.

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Carotid Artery Surgery

A. R. Naylor and W. C. Mackey
250 × 190 mm. Pp. 408 Illustrated 2001 London WB Saunders £60.00.

I rarely buy books these days and the fact that I went out and bought this one with my own money long before I was asked to review it is really the best personal accolade I can pay the editors and their contributors. Any surgeon or interventional radiologist who deals with carotid artery disease will want to have this book on his or her shelf, as will many physicians who deal with carotid surgeons or interventional radiologists. The 30 chapters are divided into four sections: patient selection, evaluation and preoperative care, operative care, and postoperative management. Each chapter title is posed as a question and each question is answered twice, once by a European and once by a North American. While there is likely to be a good deal of consensus among the Americans, it would be a mistake to think that there is a truly pan-European view of carotid surgery. Nevertheless, it is fascinating and not a little disconcerting to observe how exactly the same data can be interpreted so differently either side of the 'pond'. This dissonance is most apparent when the question of surgery for asymptomatic disease is discussed. The surgical contribution is well balanced and authoritative but I would like to have seen greater input from non-surgeons, such as neurologists, stroke physicians and interventional radiologists. Nowadays, nothing stands still for very long in medicine and that is certainly true of carotid artery surgery. With several more randomized controlled trials underway, I hope that the editors are already working on a second edition.

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Scientific Surgery

Arosio E, Ferrari G, Santoro L, Gianese F, Coccheri S for the Mesoglycan Venous Insufficiency Group. A placebo controlled, double-blind study of mesoglycan in the treatment of chronic venous ulcers. *Eur J Vasc Endovasc Surg* 2001; **22:** 365–72.

The analysis included 183 patients. After 24 weeks, healing rates were significantly greater with mesoglycan (97 per cent) than placebo (82 per cent), *P* = 0·05

Boccasanta P, Capretti PG, Venturi M, Cioffi U, De Simone M, Salamina G *et al.* Randomized controlled trial between stapled circumferential mucosectomy and conventional circular haemorrhoidectomy in advanced haemorrhoids with external mucosal prolapse. *Am J Surg* 2001; **182:** 64–8.

Clinical outcomes and complications were similar in this trial including 80 patients. The stapled procedure, however, was quicker to perform, reduced hospital stay (mean 2 *versus* 3 days, *P* < 0·01) and accelerated return to work (mean 8 *versus* 15 days, *P* < 0·001).

Villanueva C, Minana J, Ortiz J, Gallego A, Soriano G, Torras X *et al.* Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. *N Engl J Med* 2001; **345:** 647–55.

The study included 72 patients in each group followed for a median of 21 months. Rebleeding was reduced by the combined medical therapy (24 *versus* 35, *P* = 0·04), but mortality rates were similar (23 *versus* 30 respectively, *P* = 0·52).

Conlon KC, Labow D, Leung D, Smith A, Jarnagin W, Coit DG *et al.* Prospective randomized clinical trial of the value of intraperitoneal drainage after pancreatic resection. *Ann Surg* 2001; **234:** 487–94.

There was no significant difference in the overall number or type of complications, but patients with a drain were more likely to develop a significant intra-abdominal abscess, collection or fistula in this study including 179 patients.

Park WY, Thompson JS, Lee KK. Effect of epidural anesthesia and analgesia on perioperative outcome. *Ann Surg* 2001; **234:** 560–71.

The study included 1021 patients who had a variety of major abdominal operations. An epidural significantly improved overall postoperative pain control. In patients who had aortic surgery, an epidural reduced the overall incidence of death and major complications (22 *versus* 37 per cent).

Nagawa H, Muto T, Sunouchi K, Higuchi Y, Tsurtia G, Watanabe T *et al.* Randomized, controlled trial of lateral node dissection *versus* nerve-preserving resection in patients with rectal cancer after preoperative radiotherapy. *Dis Colon Rectum* 2001; **44:** 1274–80.

In the 51 patients studied, there was no effect on survival if the lateral pelvic lymph nodes and autonomic nerves were spared, but urinary and sexual function was improved.

Melling AC, Ali B, Scott EM, Leaper DJ. Effects of preoperative warming on the incidence of a wound infection after clean surgery: a randomized controlled trial. *Lancet* 2001; **358:** 876–80.

Some 421 patients having clean elective surgery were randomized to warming (either by local blanket or systemic heating) or control groups. Warming reduced the wound infection rate from 14 to 5 per cent (*P* = 0·001).

Cascinelli N, Belli F, MacKie RM, Santinami M, Bufalino R, Morabito A. Effect of long-term adjuvant therapy with interferon alpha-2a in patients with regional node metastases from cutaneous melanoma: a randomized trial. *Lancet* 2001; **358:** 866–9.

This multicentre study included 424 patients. The 5-year survival rate (35 per cent with interferon *versus* 37 per cent for surgery alone) and the disease-free survival rate (27·5 *versus* 28·4 per cent, respectively) were similar.

Seidenfeld J, Piper M, Flamm C, Hasselblad V, Armitage JO, Bennett CL *et al.* Epoetin treatment of anaemia associated with cancer therapy: a systematic review and meta-analysis of controlled clinical trials. *J Natl Cancer Inst* 2001; **93:** 1204–14.

The meta-analysis included 12 randomized trials; epoetin reduced the need for blood transfusion but the trials were judged too small to show an effect on quality of life.

Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN *et al.* Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; **345:** 725–30.

The trial included 556 patients randomly allocated fluorouracil and leucovorin with radiotherapy after resection surgery. A median 27 months after surgery alone, the hazard ratio of death was 1·35 (*P* = 0·005) and for relapse was 1·52 (*P* < 0·001). A total of 32 per cent had toxic effects, and three patients died from side-effects of chemoradiotherapy.

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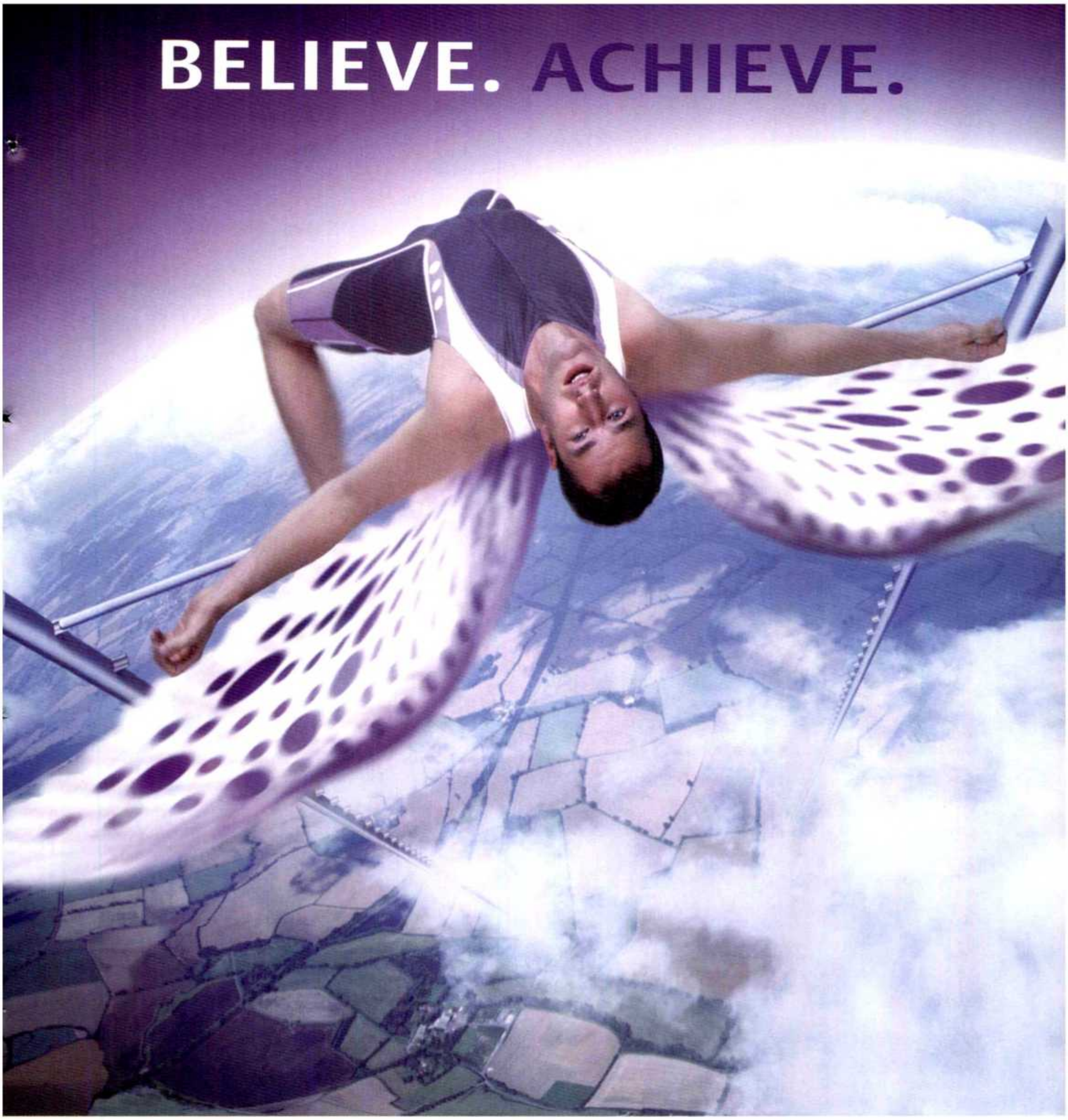
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Contents

British Journal of Surgery

Volume 89, Issue 3, March 2002

Obituary

257 **Professor J. R. Farndon**

Announcement

258 **A change of Editors**

Leading article

259 **Treatment of axillary hyperhidrosis**
M. Naumann and H. Hamm
Surgery is not the first-line therapy

Reviews

262 **Anti-human epidermal growth factor receptor 2 monoclonal antibody therapy for breast cancer**
D. S. Leonard, A. D. K. Hill, L. Kelly, B. Dijkstra, E. McDermott and N. J. O'Higgins
The pros and cons of a novel chemotherapeutic agent

272 **Early detection of colorectal cancer using high-magnification chromoscopic colonoscopy**
D. P. Hurlstone, T. Fujii and A. J. Lobo
A technique already well established in Japan

Randomized trials

283 **Randomized clinical trial of screening for abdominal aortic aneurysm in women**
R. A. P. Scott, S. G. Bridgewater and H. A. Ashton
Neither clinically indicated nor economically viable

286 **Randomized clinical trial of no wound drains and early discharge in the treatment of women with breast cancer**
A. D. Purushotham, E. McLatchie, D. Young, W. D. George, S. Stallard, J. Doughty, D. C. Brown, C. Farish, A. Walker, K. Millar and G. Murray
Drains delay discharge home

293 **Randomized clinical trial of non-mesh *versus* mesh repair of primary inguinal hernia**
W. W. Vrijland, M. P. van den Tol, R. W. Luijendijk, W. C. J. Hop, J. J. V. Busschbach, D. C. D. de Lange, D. van Geldere, A. B. Rottier, P. A. Vegt, J. N. M. IJzermans and J. Jeekel
Mesh repair is superior

Original articles

298 **Dynamic nature of early organ dysfunction determines outcome in acute pancreatitis**
A. Buter, C. W. Imrie, C. R. Carter, S. Evans and C. J. McKay
Progressive organ dysfunction increases mortality

303 **Phase I study of percutaneous cryotherapy for colorectal liver metastasis**
A. Huang, J. M. McCall, M. D. Weston, P. Mathur, H. Quinn, D. C. Henderson and T. G. Allen-Mersh
Dual probe cryotherapy is promising

311 **Estimation of prognosis after hepatectomy for hepatocellular carcinoma**
W.-C. Lee, L.-B. Jeng and M.-F. Chen
The number of risk factors present reliably correlates with disease-free and overall survival

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317 **Right-lobe live donor liver transplantation improves survival of patients with acute liver failure**
C. L. Liu, S. T. Fan, C. M. Lo, B. H. Yong, A. S. M. Fung and J. Wong
An important option in adults with acute liver failure

323 **Incidence and pattern of long saphenous vein duplication and its possible implications for recurrence after varicose vein surgery**
N. E. Corrales, A. Irvine, C. L. McGuinness, R. Dourado and K. G. Burnand
Could explain the high incidence of recurrent varicose veins

327 **Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer**
A. Wibe, P. R. Rendedal, E. Svensson, J. Norstein, T. J. Eide, H. E. Myrvold, O. Søreide on behalf of the Norwegian Rectal Cancer Group
Circumferential margin determines local recurrence

335 **Breast reconstruction in the United Kingdom and Ireland**
C. J. Callaghan, E. Couto, M. J. Kerin, R. M. Rainsbury, W. D. George and A. D. Purushotham
May be underused

341 **Late results of selective axillary surgery based on contact cytology in women with operable breast cancer**
M. Burke, K. I. Burke, S. Boyle, K. Shah, A. B. Price and C. Zammit
A possible alternative to sentinel node biopsy?

344 **Surgical workload and outcome after resection for carcinoma of the oesophagus and cardia**
E. W. Gillison, J. Powell, C. C. McConkey and R. T. Spychal
No significant relation between volume and outcome

349 **Expandable metallic stents for palliation of malignant pyloric and duodenal obstruction (short note)**
A. G. Shand, D. C. Grieve, J. Brush, K. R. Palmer and I. D. Penman
Effective palliation possible

351 **Ultrasonography is superior to plain radiography in the diagnosis of pneumoperitoneum**
S.-C. Chen, Z.-S. Yen, H.-P. Wang, F.-Y. Lin, C.-Y. Hsu and W.-J. Chen
A review of 188 patients with suspected perforation

355 **Treatment and outcome of pancreatic venous graft thrombosis after kidney–pancreas transplantation**
R. Gilabert, L. Fernández-Cruz, M. I. Real, M. J. Ricart, E. Astudillo and X. Montaña
Rescue is possible in some patients

361 **Postoperative enterococcal infection after treatment of complicated intra-abdominal sepsis**
A. Sitges-Serra, M. J. López, M. Girvent, S. Almirall and J. J. Sancho
Enterococci are commonly isolated in patients with peritonitis

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368 **Correspondence**

371 **Book reviews**

374 **Scientific surgery**

375 **Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland abstracts**

383 **Instructions to authors**

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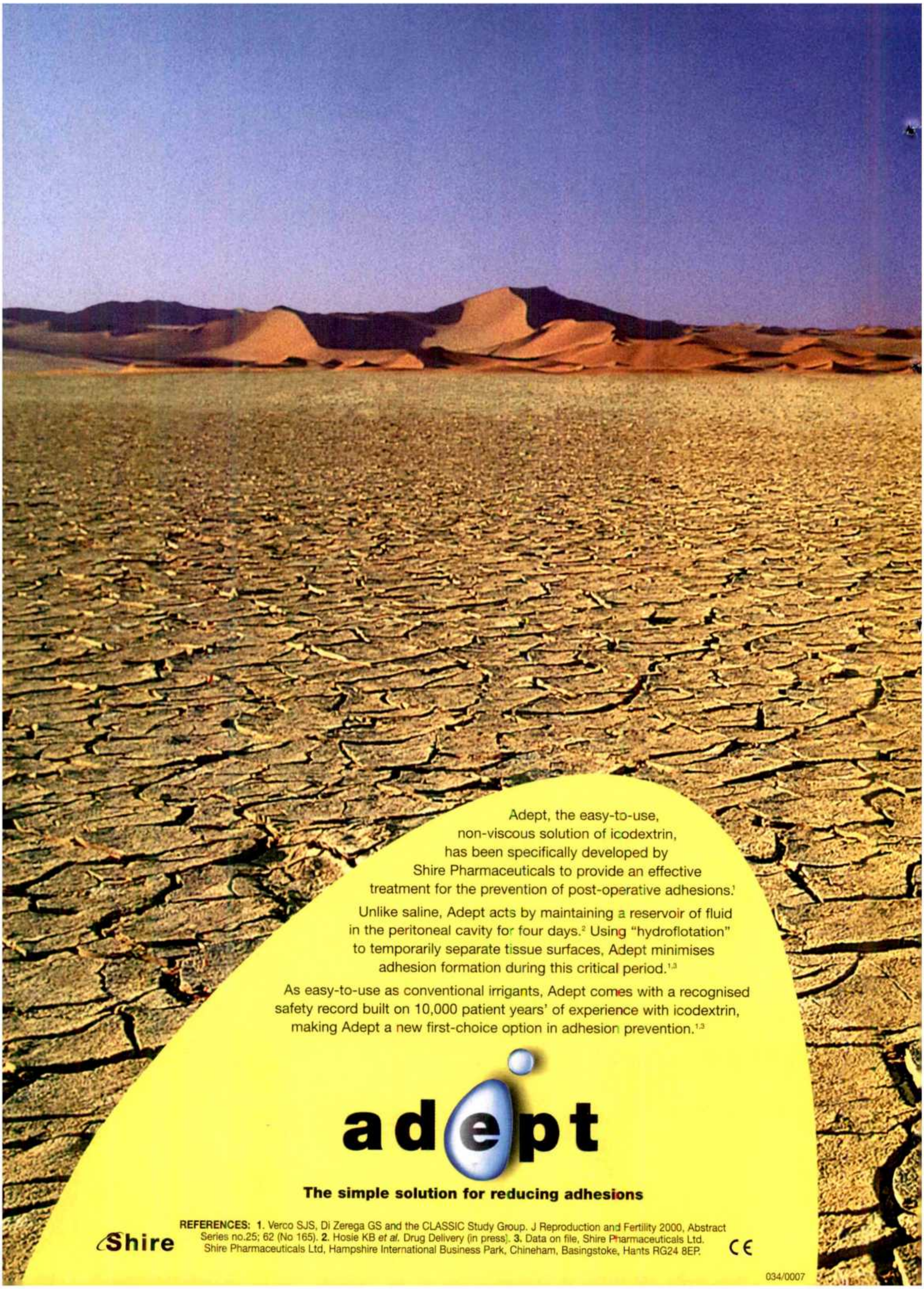

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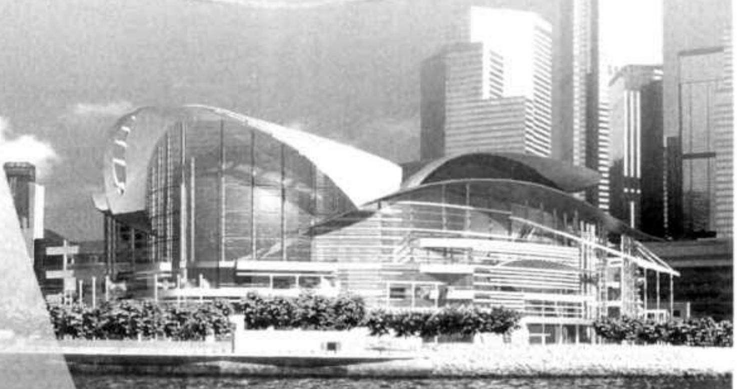

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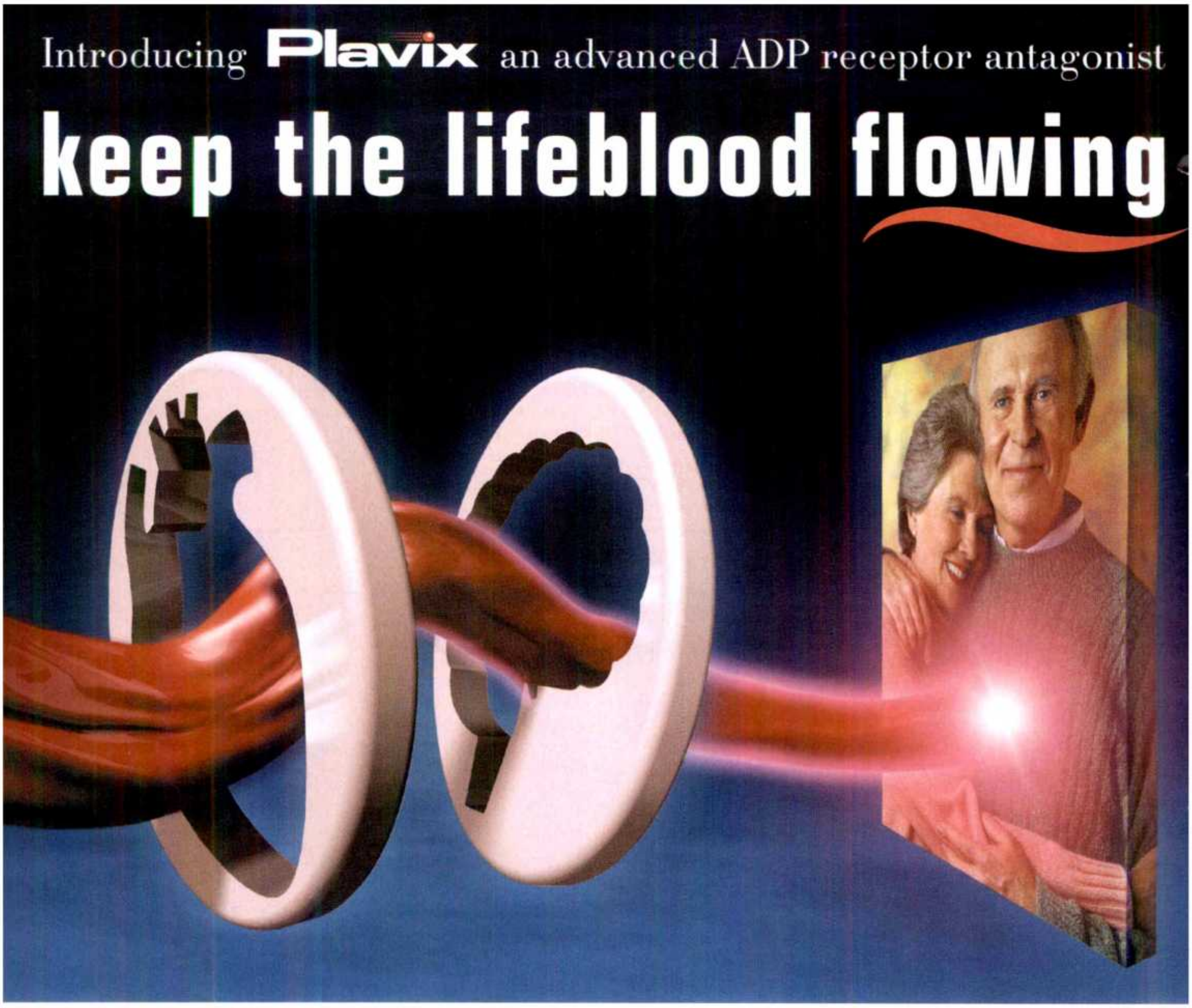
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PLA 01/182

Professor J. R. Farndon

It is with great sadness that we announce the sudden and unexpected death of Professor John R. Farndon of Bristol on 6 February 2002. John's association with *BJS* goes back as far as 1989, when he was appointed as Associate Editor, and he had been involved with the editorial process from then till now, with only a brief gap between 1995 and 1996 when he held office in the British Journal of Surgery Society (the owners of the title) as one of its vice chairmen. After 1997, John acted as Joint Editor (with John Murie) and managed *BJS* through a period of both change and success. He demitted that office just before his untimely death and was preparing to follow Mr Christopher Russell as Chairman of the British Journal of Surgery Society after its Annual General Meeting in May 2002.

As many readers will know, John's massive efforts on behalf of international surgery were not confined to *BJS*. *Inter alia*, he was Vice-President Elect of the Association of Surgeons of Great Britain and Ireland, and was to take office as Vice-President after the next Annual Scientific Meeting of that association, again in May of this year. It was expected that he would have become President in 2004.

John Farndon was a man who handled a massive workload and who shouldered great responsibilities, seemingly without effort – and always without complaint. His tragic early death will be felt keenly by his fellow professionals, not least by those of us whom he befriended at *BJS* and Blackwell Publishing. We have lost not just a great colleague but a good friend. On behalf of the Journal and its publishers, we offer our deepest sympathies to his family.

J. A. Murie
Editor-in-Chief, The *British Journal of Surgery*

R. C. G. Russell
Chairman, The British Journal of Surgery Society

A change of Editors

Alert readers will already have noticed a change in the editorship of the Journal intimated on the front cover and on the banner page (page i). A significant part of this change involves the loss of Professor John Farndon from the editorial team; this planned change coincided tragically with John's untimely death last month.

The British Journal of Surgery Society has appointed two new members to the Editorial Team: Professor Derek Alderson, a Bristol-based colleague of John Farndon, and Professor Matthias Rothmund of Marburg, Germany, the journal's first Editor from continental Europe. Both Derek and Matthias have served the journal well as enthusiastic referees over many years and we welcome them warmly as colleagues at *BJS*.

The Editors

Leading article

Treatment of axillary hyperhidrosis

M. Naumann and H. Hamm*

Departments of Neurology and *Dermatology, University of Wurzburg, Josef Schneider Strasse 11, 97080 Wurzburg, Germany
(e-mail: naumann@mail.uni-wuerzburg.de)

Focal axillary hyperhidrosis is a common condition that often affects many features of daily life. Its aetiology is so far unknown, but it is mostly young adults who are affected. If conservative treatment options, such as the application of aluminium salts or oral anticholinergics, have failed to control excessive sweating, a surgical approach may be considered. This may include local excision or curettage of axillary sweat glands, or endoscopic transthoracic sympathectomy (ETS). Recently, local injections with botulinum toxin type A (BTX-A) have proved a novel and minimally invasive treatment option for focal axillary hyperhidrosis. This article summarizes current knowledge of these treatment alternatives and provides a risk–benefit consideration.

Surgery

Local surgical management of axillary hyperhidrosis aims to eliminate as many eccrine sweat glands as possible within the vault of the axilla, while preserving, as far as possible, its normal appearance and the mobility of the arm. The simplest and most effective method is the *en bloc* excision of the entirety of the sweating area, but this inevitably leads to large and unsightly scars. To overcome this disadvantage a wealth of various surgical techniques has been proposed since the early 1960s. These include partial resection of axillary skin and subcutaneous tissue, removal of subcutaneous tissue without removing skin, shaving procedures, curettage, suction curettage, cryosurgery, and combinations of these methods. Depending on the individual technique used, bleeding, haematoma, seroma, wound infection, skin necrosis, prolonged wound healing, prominent scarring, wound contracture and restriction of arm movement may occur. Curettage and suction curettage techniques are usually performed under local anaesthesia, and appear to be superior to other procedures with regard to cosmetic results and complication profile[1,2]. However, while the operative elements of the many competing approaches are often described in detail, only limited information is available on long-term outcome and patient satisfaction. While it may be concluded that there is a place for local surgical procedures in the treatment of axillary hyperhidrosis, their importance in terms of evidence-based medicine is difficult to assess.

Interruption of the transmission of sympathetic nerve impulses from ganglia to nerve endings was introduced in the treatment of hyperhidrosis as early as 1920. However, the traditional open access to the thorax had considerable potential for severe complications and caused sizeable scars. Open surgery has since been superceded by ETS, which has been shown to be more or less equally effective but much less invasive. With the spread of minimally invasive surgical techniques and video assistance, ETS has gained broad acceptance in the past decade. The usual method is for thoracic sympathetic ganglia T2 and T3 to be destroyed by electrocautery for treatment of palmar hyperhidrosis, with the addition of T4 for axillary hyperhidrosis. While ETS (without removal of ganglia) seems as or almost as effective as more extensive traditional sympathectomy, randomized trials are lacking[3].

In about 98 per cent of patients with palmar hyperhidrosis immediate and complete anhidrosis is achieved, with only low rates of recurrence. Axillary hyperhidrosis does not appear to respond as well to the procedure. A number of significant complications may accompany definitive cure, such as arterial bleeding (possibly requiring conversion to open thoracotomy), intercostal vein bleeding, haemothorax, pneumothorax and chylothorax, pleural adhesion or effusion, peripheral nerve injury, chronic postoperative pain and discomfort, and complete or incomplete Horner's syndrome[4]. While these complications are rare, compensatory sweating (mainly of the back, abdomen and legs) occurs regularly, and gustatory sweating affects up to half of the patients[3]. Both compensatory and gustatory sweating may be severe enough to cause a handicap that is as troublesome as the original hyperhidrosis[3,5]. It is also worth noting that patients who are treated for axillary hyperhidrosis are significantly less satisfied with the ETS procedure than those treated for palmar involvement[3]. In one review[5] of 39 patients with excessive axillary sweating alone only 13 patients were satisfied with ETS; 26 patients were partially satisfied or dissatisfied. In view of the high risk of compensatory sweating, the potential morbidity associated with surgery and the documented low level of patient satisfaction, ETS provides a less than optimum treatment option, particularly for axillary hyperhidrosis.

Botulinum toxin

BTX-A is a novel and minimally invasive treatment option for focal hyperhidrosis. It is injected intradermally into the hyperhidrotic areas of the axillae, the palms or the forehead at multiple sites, and acts by temporarily blocking the release of acetylcholine from cholinergic sudomotor fibers. Two large placebo-controlled, double-blind trials[6,7] and several open-label studies have clearly documented the beneficial effect of botulinum toxin treatment through reduction of sweat secretion[6,7] and improvement of quality of life[8] in patients suffering from axillary hyperhidrosis. A large double-blind, placebo-controlled study enrolled 320 patients, and evaluated the safety and efficacy of intradermal administration of the agent (50 units BOTOX® (Allergan, Irvine, California, USA) per axilla) *versus* placebo in the treatment of bilateral primary axillary hyperhidrosis[6]. Patients were followed for 16 weeks. At week 4, 93·8 per cent of patients treated with BTX-A were classified as responders (over 50 per cent reduction in sweat production from baseline gravimetric measurement), compared with 35·9 per cent of the placebo group ($P < 0{\cdot}01$). The mean percentage reduction in sweat production at this time was 83·5 per cent in the BTX-A group compared with only 20·8 per cent in the placebo group ($P < 0{\cdot}01$).

Some 207 patients were followed for a further 12 months and received up to three more BTX-A treatments. Response rates and satisfaction with treatment remained consistently high, with no diminution of effect with repeated injections[9]. The mean duration of benefit was about 7 months after a single treatment session but about 28 per cent of patients required no more than one treatment, indicating a long-lasting benefit of over 16 months in a substantial proportion of patients. No major side-effects occurred in the whole period of 16 months (controlled and follow-up study). BTX-A treatment markedly improved the quality of life of patients afflicted with hyperhidrosis (Hyperhidrosis Impact Questionnaire© and the Medical Outcomes Trust SF-12 Health Survey™ (SF-12)). At baseline, participants reported a marked negative impact of their hyperhidrosis on various measures, including state of mind, emotional status, comfort in social situations, productivity at work, number of clothing changes needed per day, and ability to engage in sex or participate in athletic activities. After treatment, significantly greater improvements were observed in all of these variables in the BTX-A group than in the placebo group ($P < 0{\cdot}01$). Patients treated with BTX-A also exhibited significantly greater improvement in the physical component summary score of the SF-12 at 16 weeks than placebo-treated patients ($P < 0{\cdot}02$). Another study of 145 patients with axillary hyperhidrosis (100/200 units Dysport® (Ipsen, Slough, UK) per axilla) obtained similar results with regard to efficacy and safety, but no quality of life or follow-up data are available[7]. These large controlled studies lent support to the reports of several previous open-label studies indicating that BTX-A is a safe and highly effective treatment for axillary hyperhidrosis. Based on the large controlled trial[6], BTX-A is now licensed for the treatment of this condition in the UK, Canada and other countries.

Conclusion

The long-term benefit of local surgical treatments for axillary hyperhidrosis is uncertain; no data from large or even controlled studies with gravimetric assessment of preoperative and postoperative sweat production are available. ETS has proved a highly effective treatment option for axillary hyperhidrosis, but it is associated with perioperative complications, including a high risk of persisting compensatory sweating. BTX-A is a simple, highly effective and safe treatment for axillary hyperhidrosis that, owing to its temporary effect of about 7 months, must be performed repeatedly. In view of these pros and cons we recommend BTX-A as first-line therapy in axillary hyperhidrosis that has proved refractory to conservative treatments. Surgery is no longer the treatment of choice for this condition[10] but it should be considered if BTX-A fails or if the patient requests it.

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Forged signatures

The *BJS* Instructions to Authors state 'A covering letter must accompany all submissions, must be signed by all authors and...'.

The editors received a letter of submission from the Tumour and Angiogenesis Research Group based in Crete on 24 July 2001. The letter of submission was signed by five authors from Crete and by two senior clinical academics based in the UK. The 'author responsible for negotiations concerning the manuscript' was Dr Alexandra Giatromanolaki and the coauthors from Greece were Drs Efthimios Sivridis, Constantinos Simopoulos, Alexandros Polychronidis and Michael I Koukourakis.

One of the editors knew the handwriting of one of the UK collaborators and recognized that this was not the usual signature. Cross-checking showed that the signature of the two UK collaborators had been forged. Dr Koukourakis wrote on 29 August requesting withdrawal of the paper from the Journal's referee process.

The current Instructions to Authors state quite clearly that all authors must sign a letter of submission. The Journal will accept letters attesting to and agreeing with the contents of a paper emanating from two sources. Separate letters of attestation could have been sent from Greece and the UK. Forging signatures is not an acceptable code of practice.

The Editors

Anti-human epidermal growth factor receptor 2 monoclonal antibody therapy for breast cancer

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Background: Advances in molecular biology and improved understanding of tumour biology have led to the development of novel treatments for cancer. Trastuzumab (Herceptin; Genentech, San Francisco, California, USA) is a monoclonal antibody directed against human epidermal growth factor receptor (HER) 2 protein, which is overexpressed in a wide variety of human cancers, including 20–30 per cent of human breast cancers. HER-2 plays an important role in oncogenic transformation, tumorigenesis and metastatic spread. Overexpression is associated with a poor prognosis and predicts a poor response to several treatment modalities.

Method: Literature relating to the monoclonal antibody was identified by a Medline literature search and by cross-referencing from the references of seminal articles on the subject. Four major clinical trials were identified and reviewed.

Results and conclusion: In clinical trials approximately 15–20 per cent of patients with HER-2-overexpressing tumours benefited from treatment with trastuzumab. In sensitive patients the antibody appeared to have intrinsic anticancer activity when given as a single agent. In combination chemotherapy it appeared to act synergistically with other agents. Ongoing research is evaluating trastuzumab in combination with numerous standard chemotherapy regimens and with other novel chemotherapeutic agents. Clinical trials have also revealed several serious side-effects of monoclonal antibody therapy. Most notable is an unpredictable cardiotoxicity, especially when used in combination with anthracycline-based chemotherapy regimens.

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Introduction

Advances in molecular biology have led to a better understanding of tumour biology which has, in turn, been followed by improved treatment and advances in patient care. Trastuzumab (Herceptin; Genentech, San Francisco, California, USA) is an example of molecular biological research that has had a speedy and useful clinical application. This is a recombinant human monoclonal antibody (Mab) directed against the human epidermal growth factor receptor (HER) 2 protein (also known as ErbB-2 or neu), which is overexpressed in a wide variety of human tumours, including 20–30 per cent of breast cancers[1,2]. This receptor is a member of the epidermal growth factor receptor (EGFR) family, a group of EGFR tyrosine kinases[3] that play an important role in controlling cell growth, survival and differentiation[4]. Amplification of the HER-2 gene and corresponding overexpression of the receptor protein has been implicated in oncogenic transformation, tumorigenesis and metastasis[5–7].

In general, breast cancers that overexpress HER-2 carry a poorer prognosis and are more resistant to chemotherapy. With the advent of trastuzumab, the HER-2 itself has become a target for therapeutic intervention. Trials of the agent as both monotherapy and in combination with other chemotherapeutic agents suggest that it has an intrinsic anticancer activity and that it may also act synergistically with other agents. Increased disease-free and overall survival rates have been recorded in HER-2-positive patients treated with trastuzumab.

Human epidermal growth factor receptor 2 status as a prognostic and predictive factor

In breast cancer, HER-2 overexpression is both an independent prognostic and a predictive factor, correlating with poor prognosis[1,2,8,9] and predicting a poor response to both chemotherapy and hormonal therapy[10–15]. Overexpression correlates with a number of recognized prognostic factors including nodal status, tumour grade[16], mitotic index and oestrogen receptor (ER)/progesterone receptor (PR)-negative status[17]. In addition HER-2 gene amplification independently predicts reduced disease-free and overall survival, and increased recurrence risk in patients with breast cancer[1,18–27]. Studies investigating ductal carcinoma *in situ* have shown that HER-2 overexpression, which occurs in 40–60 per cent of cases[28–31], also tends to be associated with a more aggressive subtype, specifically high-grade comedo type, and is more likely to be associated with an invasive component[29,30,32,33]. Breast tumours that overexpress HER-2 are, in general, more resistant to hormonal and chemotherapeutic agents. Several studies dating from 1992 have shown that HER-2 overexpression predicts a lack of response to both hormonal therapies, specifically tamoxifen[34–38] and CMF (cyclophosphamide–methotrexate–5-fluorouracil) chemotherapy[39–41]. However, there has been some evidence to suggest that these tumours have a relatively increased sensitivity to anthracycline-based regimens[42,43].

Assessment of human epidermal growth factor receptor 2 status

Given its importance as a prognostic and predictive factor, and its development as a target for immunotherapy, accurate assessment of the HER-2 status of breast cancer has become clinically valuable. Both the presence of HER-2 overexpression and the degree to which it is overexpressed are important predictive factors of response to anti-HER-2 Mab treatment[44]. Currently the two most common methods of assessment in the clinical setting are immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH).

Immunohistochemistry

IHC is the most widely used method of assessment. It is rapid, specific and relatively simple to perform with commonly available equipment. Paraffin-embedded tissue samples are stained for HER-2 protein and assessed for strength of staining. Staining is generally graded qualitatively on a scale from 0 to 3+ based on comparison with cell-line controls of known receptor density (*Table 1*). Patients with tumours scoring 3+ generally respond best to trastuzumab therapy, although occasional responses have occurred in those with low IHC scores, according to the manufacturer's product information insert. The risk of operator-dependent variation and the semiquantitative nature of its results are the major disadvantages associated with IHC assessment. In addition, it is unreliable in archived specimens, giving inappropriately low results[45], and in needle biopsies in which cut cells can lead to artefactual, inappropriately high, results.

Inconsistencies in IHC assessment of HER-2 status can also arise owing to differences in laboratory protocols. Sensitivity varies considerably depending on the particular Mab used in the staining[46,47] and the techniques used in preparation of the specimen (duration and type of fixation, thickness of the tissue slice, and paraffin temperature during embedding)[48,49]. Variations in technique are particularly problematic where HER-2 status is assessed only on specimens referred from outside institutions.

Standardization of IHC protocols is essential to ensure accurate assessment of HER-2 status. Commercially available HER-2 IHC assay kits (HercepTest®; DAKO, Carpinteria, California, USA) provide a detailed standard procedure and control slides against which samples may be compared. Rigid adherence to these guidelines can facilitate the standardization of preparation and staining protocols.

Fluorescence *in situ* hybridization

FISH detects amplification of the HER-2 gene rather than overexpression the HER-2 protein. Its advantages over IHC include higher specificity and sensitivity, a quantitative result that eliminates operator-dependent variation, the ability to test very small tissue samples and good reproducibility[50]. Unfortunately, most laboratories are not equipped to assess HER-2 status using FISH; the procedure is time consuming and complicated, and the required equipment expensive.

FISH predicts prognosis and response to anti-HER-2 Mab therapy in HER-2-positive patients more accurately than IHC. In a minority of patients HER-2 overexpression occurs in the absence of HER-2 gene amplification[51,52]. In this subgroup HER-2 status does not correlate with prognosis[53], nor do these patients respond to anti-HER-2 Mab therapy[54]. This suggests that HER-2 gene amplification as detected by FISH is of greater therapeutic significance than HER-2 overexpression as detected by IHC.

Table 1 Control cell-line human epidermal growth factor receptor 2 density determined by immunohistochemical staining

Stain score	No. of receptors per cell	HER-2 status
0	20 000	Negative
1+	100 000	Negative
2+	500 000	Weakly positive
3+	2000 000	Strongly positive

HER-2, human epidermal growth factor receptor 2

Immunohistochemistry *versus* fluorescence *in situ* hybridization

In general the concordance between IHC and FISH assessments of HER-2 status is excellent. In HER-2 status assessment for trastuzumab-based clinical trials, the concordance between IHC and FISH was 82 per cent[54]; these results were reproduced in two independent studies not associated with the trials themselves[55,56]. IHC is the assessment test of choice at present, largely because of its greater availability, but as FISH and other DNA detection techniques become more economically viable and widely available they are likely to replace IHC in routine clinical use. Currently, reassessment of weakly positive (2+) IHC results by FISH is performed in some centres that have the necessary resources.

Mechanism of action

Anti-HER-2-directed therapy, such as trastuzumab, attempts to improve the disease course of HER-2-positive breast cancer by inhibiting the abnormal function of the overexpressed receptors. The mechanism of action is not yet clear, although a number of possibilities has been proposed including: (1) direct antagonism of the overexpressed receptors in the manner of a false ligand[57,58]; (2) acceleration of HER-2 internalization and degradation[59,60]; (3) targeting of abnormal cells for destruction by the cell-mediated immune system[58,61–65]; (4) downregulation of angiogenic factors such as vascular endothelial growth factor (VEGF)[66]; and inhibition of DNA repair in abnormal cells[67,68].

Trastuzumab slows the overall rate of proliferation of breast cancer cell lines that overexpress HER-2 (SK-BR-3)[57]. It causes a dose-dependent reduction in the proportion of cells undergoing S phase, during which proteins are synthesized and DNA is replicated, and proportionally increases the percentage of cells in G0/G1. In addition, anti-HER-2 Mabs directly inhibit the normal growth-signalling properties of HER-2[58]. This suggests that trastuzumab acts in a cytostatic, inhibitory rather than in a directly cytocidal manner.

Anti-HER-2 Mabs induce downregulation of the HER-2 protein. Ultimately this leads to reversal of the transformed phenotype of the HER-2-overexpressing cells. A role for tyrosine autophosphorylation in downregulation has been proposed, but studies have produced conflicting results[59,60]. The effect of anti-HER-2 Mabs on tyrosine autophosphorylation correlates poorly with antitumour activity, suggesting the existence of another mechanism. Trastuzumab supports antibody-dependent cell-mediated cytotoxicity against HER-2-overexpressing breast tumour cell lines[61–64] through the recruitment of natural killer cells[58]. In addition, complement activation against HER-2-positive breast tumour tissue has been demonstrated in mouse xenograft models[65]. Trastuzumab-treated HER-2-positive breast cancer cells display increased susceptibility to cisplatin[68] and radiation injury[67], suggesting inhibition of DNA repair mechanisms. This receptor-enhanced sensitivity is not found in cells that express normal amounts of HER-2[69]. The relative roles, if any, of these proposed mechanisms of action remains to be elucidated, as do many of the specific details of the antitumour effects of trastuzumab.

Clinical trials

The role of trastuzumab in the treatment of breast cancer, both as a single agent and in combination with other chemotherapeutic agents, has been evaluated in a number of clinical trials (*Table 2*).

Table 2 Selected clinical trials of trastuzumab

Reference	Year	Trial type	No. of patients	Monotherapy	Combination therapy	Response	Mean time to progression (months)	Survival advantage (months)
Baselga *et al.*[70]	1996	Phase II	43	Yes		1 (complete) 4 (partial)	—	—
Cobleigh *et al.*[44]	1999	Phase II	222	Yes		8 (complete) 26 (partial)	3·1	—
Slamon *et al.*[71]	1998	Phase III	469	No	Control (*n* = 234)	85 (36)	5·5	—
					Trastuzumab plus paclitaxel (*n* = 89)	51 (57)	7·1	3·7*
					Trastuzumab plus cyclophosphamide plus anthracycline (*n* = 146)	95 (65)	9·0	8·9*
Pegram *et al.*[72]	1999	Phase II	39	No	Trastuzumab plus cisplatin	0 (complete) 9 (partial)	5·3	—

Values in parentheses are percentages. **P* not significant (log rank test)

Anti-human epidermal growth factor receptor 2 monotherapy

The earliest phase II single-agent trial demonstrated an overall response rate of 12 per cent in patients with extensively pretreated HER-2-positive metastatic disease. Of the 43 patients evaluated, one had a complete response to therapy and four others had a partial response[70].

A larger, multicentre, single-arm phase II trial generated similar results. Some 222 women with extensively pretreated metastatic breast cancer were treated with intravenous trastuzumab monotherapy in 54 centres across seven countries (4 mg/kg initial dose followed by 2 mg/kg weekly infusions)[44]. The overall response rate was 15 per cent, based on intention to treat. The 222 patients were monitored for tumour response; eight had a complete response and a further 26 had a partial response. The 34 responders also showed improvement in several secondary endpoints. The median duration of response was 9·1 months, significantly longer than 5·2 months from previous chemotherapeutic regimens. The median survival of patients responding to trastuzumab monotherapy was 13 months, with a median time to treatment failure of 11 months. This compared favourably with the median time to treatment failure of 5·4 months for previous chemotherapeutic regimens.

Eighty-five per cent of patients studied did not respond to anti-HER-2 monotherapy. Among all treated patients the median time to disease progression was 3·1 months, and the median time to treatment failure was 2·4 months. As this was a single-arm trial, no control subjects exist with whom direct comparison may be made. However, comparison with previous treatment regimens received by these patients suggests that trastuzumab monotherapy does have a significant therapeutic effect, producing objective tumour response in selected cases of advanced, previously treated, HER-2-positive breast cancer.

Anti-human epidermal growth factor receptor monoclonal antibody in combination chemotherapy

Several phase II and III trials of trastuzumab as an agent in first-line combined chemotherapy for patients with HER-2-positive metastatic breast cancer have been reported. In the largest phase III trial, the effect of this agent in combination with standard chemotherapy was assessed in a cohort of 469 patients with HER-2-positive metastatic breast cancer[71,73]. None of these patients had previously received chemotherapy for metastatic disease. The study comprised four arms: two experimental groups that received trastuzumab in addition to standard chemotherapy and two control groups that received standard chemotherapy alone. Patients who had not previously received anthracycline chemotherapy for treatment of the primary tumour were treated with an anthracycline plus cyclophosphamide, with or without trastuzumab. Patients who had been treated previously with anthracyclines received paclitaxel alone or in combination with trastuzumab. The study considered time to disease progression as its primary endpoint, while also considering objective tumour response rate, response duration, time to treatment failure and 1-year survival as secondary endpoints.

At 14 months' follow-up, the addition of trastuzumab was associated with a 61 per cent improvement in time to disease progression, from 4·6 to 7·6 months. The percentage improvement was greater in patients receiving paclitaxel plus trastuzumab (69 per cent) than in those receiving an anthracycline plus cyclophosphamide and trastuzumab (38 per cent). Despite the lower percentage improvement, the median time to disease progression remained greater in patients treated with an anthracycline and cyclophosphamide plus trastuzumab (9·0 *versus* 7·1 months). However, it should be noted that patients in the paclitaxel subgroup were more likely to have other adverse prognostic factors.

Secondary endpoints were also improved in association with trastuzumab. At a median follow-up of 25 months a significant advantage in median overall survival was demonstrated in the cohort receiving trastuzumab (25·4 versus 20·9 months). Again, patients who received trastuzumab in combination with paclitaxel demonstrated a greater percentage improvement than those receiving an anthracycline and cyclophosphamide when compared with their respective controls. Tumour response rate in association with trastuzumab was almost double that of standard chemotherapy alone (62 *versus* 36 per cent). Non-significant improvements in time to treatment failure and survival were also noted. Overall, the results suggest that addition of trastuzumab to first-line chemotherapeutic regimens improves survival in patients with metastatic breast cancer.

Multicentre phase I and II trials have assessed the efficacy of cisplatin and trastuzumab in combination[72]. In the phase II trial, 39 patients with chemoresistant HER-2-overexpressing tumours were given an initial intravenous loading dose of 250 mg trastuzumab followed by a regimen of 100 mg trastuzumab, plus 75 mg/m^2 cisplatin every 28 days. After 70 days of treatment, 37 of the 39 patients were evaluable for clinical response. Nine patients (24 per cent) had an objective clinical response while a further nine had stable disease. This response rate compared well with that reported for cisplatin alone (7 per cent) or trastuzumab alone (15 per cent)[70,74]. Patients with responsive or stable disease were enrolled in a maintenance phase until disease progression or intolerable toxicity occurred. The median response duration among responders was 5·3 months.

Other studies evaluating trastuzumab in combination with standard chemotherapeutic regimens have yielded similar results; the addition of trastuzumab to standard chemotherapeutic regimens increases their efficacy. Improvements are noted in a number of objective endpoints: time to disease progression, objective tumour response rate, response duration and time to treatment failure. Concurrent administration of trastuzumab and standard chemotherapy causes greater improvement in these endpoints than sequential administration, suggesting a synergistic rather than an additive relationship[73].

Adverse effects and safety

Data collected over the course of phase II and III trials indicate that trastuzumab is generally well tolerated[44,71,73].

Minor events and infusion reactions

During single-agent trials most patients (99 per cent) experienced at least one adverse event, but most of these were minor. They included pain (48 per cent), asthenia (46 per cent) and headache (26 per cent). Infusion-associated fevers and chills occurred in approximately 40 per cent of patients. In general these reactions were treated successfully with mild analgesics and did not recur after the first infusion.

The combined incidence of severe infusion reactions associated with trastuzumab administration was three per 1000 treated. Reactions were characterized by respiratory symptoms including dyspnoea, bronchospasm and respiratory distress, and occurred within 2 h of infusion. Some were associated with an anaphylactoid reaction with hypertension and rash. Severe reactions were treated with antihistamines, β-agonists, corticosteroids and oxygen as necessary. Despite treatment, infusion-related deaths were reported as approximately four per 100 000 treated. More than one-third of patients suffering a severe infusion reaction were successfully rechallenged with trastuzumab without concomitant antihypersensitivity treatment.

In combination chemotherapy trials a similar incidence of minor adverse events and infusion-associated fevers and chills was reported. However, the side-effect profile of the combination regimens tended to be dominated by the side-effects of the other chemotherapeutic agents.

Cardiotoxicity

Unexpected, unpredictable cardiotoxicity was noted during phase II and III clinical trials of trastuzumab. Its effects ranged from an asymptomatic decrease in left ventricular ejection fraction, to cardiomyopathy, to symptomatic congestive cardiac failure. Development of cardiotoxicity was associated with a number of independent risk factors including previous or concomitant anthracycline use and coexisting cardiac risk factors.

In one multinational study 6–9 per cent of patients receiving trastuzumab monotherapy developed cardiotoxicity[44]. Of these, all but one had received previous anthracycline chemotherapy. Symptomatic heart failure developed in 9–11 per cent of patients receiving trastuzumab plus paclitaxel, compared with 1–4 per cent of those receiving paclitaxel alone. In patients receiving anthracyclines the increase was far greater: 26–28 per cent of patients receiving trastuzumab plus an anthracycline and cyclophosphamide developed heart failure compared with 6–10 per cent of those receiving an anthracycline and cyclophosphamide alone[71,73]. Standard conservative management of cardiac dysfunction with angiotensin-converting enzyme inhibitors, diuretics and cardiac glycosides allowed most patients suffering from symptomatic cardiotoxicity to continue treatment with trastuzumab. In most cases prompt and effective management led to reversal of the dysfunction with no residual deficit.

It has been postulated that HER-2 pathways may be involved in myocyte repair and that concomitant administration of trastuzumab may interfere with the repair of anthracycline-damaged myocytes. Further research into the exact function of HER-2 and the mechanism of action of trastuzumab may clarify the situation.

Ongoing trials

Trastuzumab as first-line monotherapy

Trastuzumab has recently being assessed as a first-line therapy for metastatic breast cancer[75]. A total of 114 HER-2-positive patients was given the drug either at high dosage (8 mg/kg initial dose followed by 4 mg/kg weekly) or in standard dosage (4 mg/kg followed by 2 mg/kg weekly). After 19 months an overall response rate of 26 per cent was observed; 6 per cent were complete responses and 20 per cent were partial. A further 12 per cent of the patients had stable disease for more than 6 months. Similar response rates were produced by the high-dose and standard-dose regimens. The survival advantage attributable to trastuzumab monotherapy was not assessed formally, but was estimated to be 24 months.

Trastuzumab in first- and second-line combination chemotherapy

A number of studies are assessing the value of trastuzumab used in combination with other established chemotherapeutic agents. Combination therapy with weekly paclitaxel has produced response rates of 75–83 per cent in patients with HER-2-positive breast cancer[76]. Other small trials are assessing trastuzumab in combination with docetaxel (response rate 33–83 per cent)[77–79], vinorelbine (response rate 71 per cent)[80] and epirubicin plus cyclophosphamide. The hope is to find an effective combination with a minimal side-effect profile.

Trastuzumab in combination with novel agents

Trastuzumab plus interleukin (IL) 2 has been evaluated in 33 patients with HER-2-overexpressing tumours[81]. Of these patients, two experienced a complete response to the combined therapy and four had a partial response. Response to therapy in this particular study appeared to be dependent on the dosage of trastuzumab. Current studies are exploring the use of low- and intermediate-dose IL-2 plus trastuzumab in patients who have failed to respond to trastuzumab monotherapy.

The role of ras proteins in the regulation of both normal and transformed cell growth is well established and can be modulated by farnesyl transferase inhibitors. R115777, a farnesyl transferase inhibitor with demonstrated clinical activity in advanced breast cancer[82], is currently being studied in combination with trastuzumab. It is hoped that targeting two separate components of abnormal proliferative signal transduction may prove effective.

Other novel combinations have been suggested. The use of EGFR kinase inhibitors such as ZD1839[83] in association with trastuzumab would target two stages in the HER-2 signalling pathway (receptor and tyrosine kinase). This combination might prove to have a greater effect than either agent alone. Humanized anti-VEGF antibody has also demonstrated antitumour activity in patients with heavily pretreated metastatic breast cancer and may prove effective in combination with trastuzumab[84].

Financial implications

Resources are limited and cost must be considered when evaluating novel treatments. The widespread use of trastuzumab for breast cancer would impose a significant financial burden on any healthcare service. The 11-week treatment regimen used by Baselga *et al.*[70] in their phase II trial of trastuzumab monotherapy for metastatic breast cancer costs approximately £3400 per patient. Those responding to initial treatment are then placed on a maintenance programme costing approximately £270 per patient per week. Similar regimens have been employed in other studies that have assessed trastuzumab as both combination and monotherapy.

At this time an assessment of the cost effectiveness of this agent is probably premature. Further research is required to maximize its effectiveness both as monotherapy and in combination with other drugs. Its role, if any, in the treatment of non-metastatic breast cancer must also be explored. Finally, further research into the nature of the interaction between trastuzumab and HER-2 may uncover a means of identifying potentially responsive tumours before beginning treatment. When these questions have been explored, the full financial implications of trastuzumab should be more apparent.

Concluding remarks

Anti-HER-2 Mab therapy represents the first success of molecular biology in the clinical setting. By binding preferentially to overexpressed HER-2 cell surface receptors, anti-HER-2 Mabs (specifically trastuzumab) decrease their oncogenic and pro-metastatic effects. It is not, however, an unequivocal success.

Single-agent trastuzumab therapy produces objective, measurable benefits in 15–20 per cent of patients with HER-2-positive breast cancer. In trastuzumab-sensitive patients with previously treated metastatic cancer, it compares favourably with more traditional agents. However, single-agent therapy confers minimal benefit to the remaining 80–85 per cent. It is unfortunately not yet possible accurately to identify sensitive tumours before treatment. For trastuzumab to become a viable single-agent treatment for breast cancer a means of preselecting the 15 per cent of patients who will respond must be developed.

When used in combination regimens trastuzumab has been shown to improve overall survival, and to increase time to disease progression and time to treatment failure in a synergistic rather than an additive manner. However, when used in combination with other chemotherapeutic agents, especially anthracyclines, the therapy is associated with increased toxicity, specifically cardiotoxicity. Ongoing research is assessing previously untried chemotherapeutic combinations, seeking to maximize efficacy while minimizing side-effects.

Despite its limitations, trastuzumab is an important addition to the chemotherapeutic armamentarium. It is not simply a novel chemotherapeutic agent, but represents an entirely new approach to chemotherapy based on molecular biology.

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Review

Early detection of colorectal cancer using high-magnification chromoscopic colonoscopy

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Background: Endoscopic techniques aimed at early detection of colorectal cancer (CRC) and its precursors, permitting targeted *in vivo* luminal treatments, have been developed by the Japanese since the early 1990s. The introduction of this new technology to the UK (i.e. magnification endoscopes) may permit earlier and more accurate diagnosis. According to Japanese data, magnification chromoscopy can be used to predict histology and invasive depth of cancer, and help in the detection of flat and depressed colonic lesions. Flat and depressed lesions are not purely Japanese phenomena: they exist with a similar incidence in the UK.

Methods: A Medline search was performed for the years 1955–2001 using the following medical subject headings and search methodology: colorectal cancer and colonoscopy or aberrant crypt foci or molecular kinetics or flat/depressed lesions or chromoscopy.

Results and conclusion: Early CRC, in the form of flat or depressed lesions, can be difficult to detect using conventional colonoscopic techniques and penetrate the colonic mucosa deeply. The implications of detecting these lesions in relation to current approaches to the prevention of CRC are profound.

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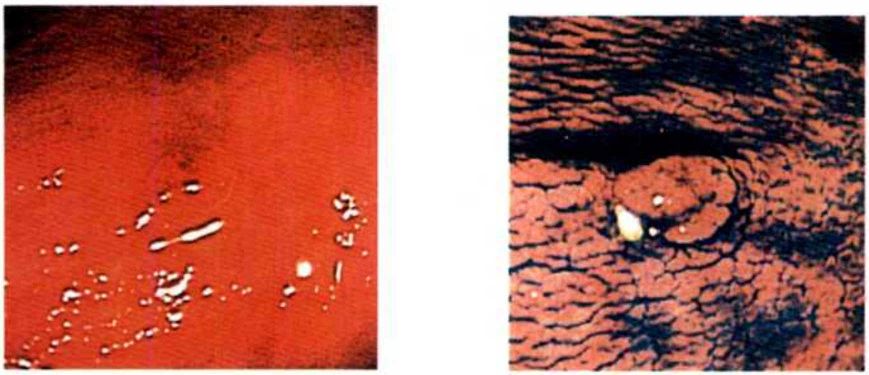
Introduction

The development of flat lesion theory and the use of chromoscopy in the diagnosis of colorectal pathology have followed a similar evolution to our understanding of gastric and early oesophageal cancers, but with a significant time lag. Concepts and diagnostic techniques that were used only for malignancy of the stomach and oesophagus have now been applied to colorectal cancer (CRC). Kariya[1] reported the first case of a depressed lesion in 1977, but until 1994, when Kudo *et al.*[2] reported a flat adenoma cohort and classification, flat and depressed lesions were thought to be phenomena unique to Japan (phantom carcinoma or Akita disease). Rembacken *et al.*[3], however, have now clearly defined a comparable incidence of flat adenomas in a large European cohort.

For the detection of large polyps and advanced CRC, chromoendoscopy and magnifying colonoscopy are not required. The strength of these techniques lies essentially in their ability to identify flat lesions whose detection with conventional colonoscopy is inadequate. Current data suggest that flat adenomas may account for more than 30 per cent of all colorectal lesions and their malignant potential may be significantly higher than that of polypoid lesions. Magnification colonoscopy complemented by mucosal dye spraying represents a worthwhile addition to conventional diagnostic tools. Most flat lesions are minute and have an innocent appearance at initial colonoscopy. Macroscopic non-magnified views commonly reveal only subtle architectural deviation, such as a modest colour change (discoloration and faint redness) or a loss of the vascular net. The use of stains, such as indigo carmine, along with magnification colonoscopy offers a quick and simple diagnostic tool in this situation.

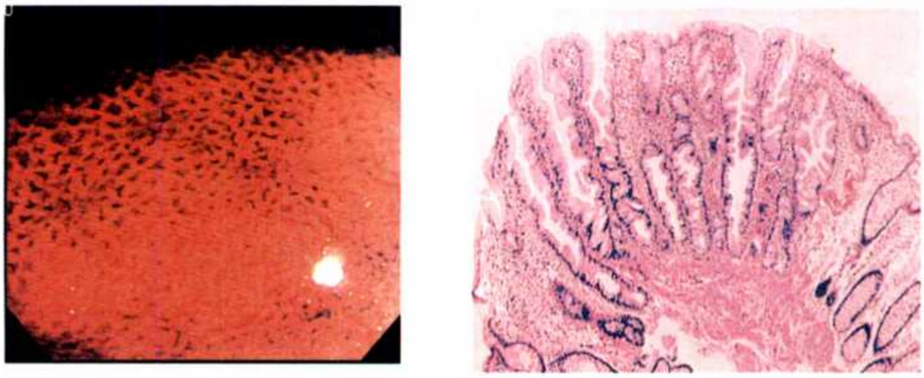
Method

A Medline search of the literature was performed for the years 1955–2001 using the following medical subject headings and search methodology: colorectal cancer and colonoscopy or aberrant crypt foci or molecular kinetics or flat/depressed lesions or chromoscopy. A total of 566 relevant papers was identified, with further articles sourced from the reference list of these papers. Additional material was obtained from recently published abstracts of meetings.



a Non-magnified

b Magnified × 20



c Magnified × 80

d Histology

Fig. 1 Kudo classification type II: this pattern has a cross- or star-shaped pit, slightly wider than normal pits. It is found in hyperplastic lesions or in mixed adenomatous–hyperplastic tissue commonly called serrated adenoma. In the latter, the pits are larger than in the hyperplastic view. Fujii classification: non-neoplastic pit pattern. **a** Non-magnified view; **b** magnified view (× 20; indigo carmine 0·2 per cent stain); **c** magnified view (× 80); **d** histological specimen showing benign hyperplasia

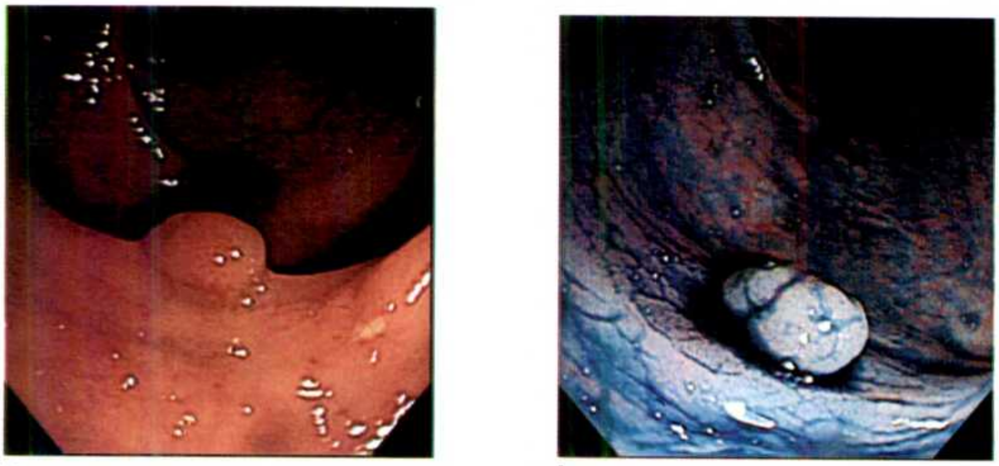
Background

CRC is the most common malignant lesion of the gastrointestinal tract and claims in excess of 20 000 lives per year in the UK[4]. Globally, the majority of cases occur in economically developed countries, particularly North America and western Europe[5]. In Japan, the incidence and mortality rates of CRC have increased markedly since the westernization of dietary habits[6]. The variation in incidence of CRC may be as high as 10–20-fold, with the highest rates of 25–35 per 100 000 in North America, western Europe and Australasia[7]. Significant supporting evidence for the influence of environment factors comes from observational studies demonstrating an increased incidence of CRC in migrants from low- to high-risk countries compared with age- and sex-matched controls[8].

Pathogenesis of colorectal cancer

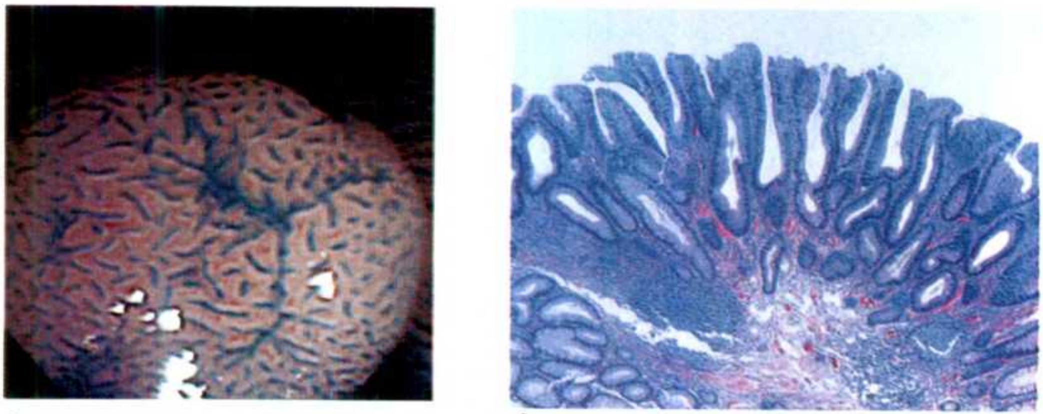
Polypoid adenoma

It is widely accepted that polypoid adenoma is the precursor of colonic adenocarcinoma[9,10]. Over a number of years, some benign adenomas develop characteristics of malignancy as they increase in size. The morphological transformation from adenoma to carcinoma is paralleled by the accumulation of numerous genetic abnormalities in oncogenes and anti-oncogenes[11]. This sequence is believed to account for about two-thirds of CRCs. This concept of the pathogenesis of CRC has enormous clinical implications as it constitutes the rationale for therapeutic intervention to prevent the disease. Colonoscopic polypectomy has been shown to reduce the incidence of CRC[12].



a Non-magnified

b Magnified × 20



c Magnified × 60

d Histology

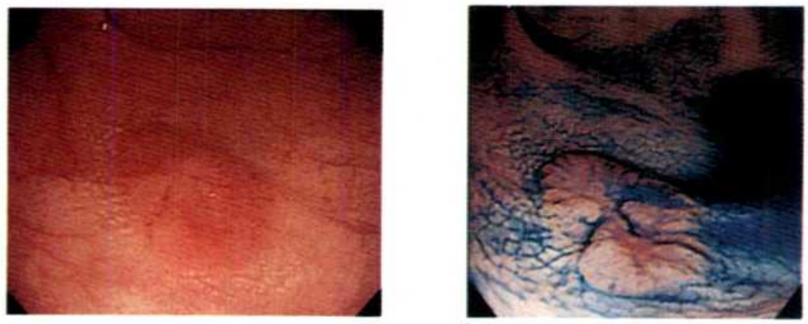
Fig. 2 Kudo classification type IIIL: long, slightly curved or oval pits, larger than normal pits. This pit pattern is usually found in adenomatous lesions. The morphology results from a dilated lumen structure with several branches finishing in the same orifice. Usually this pattern is associated with low to moderate dysplasia. Fujii classification: neoplastic, non-invasive pit pattern. **a** Non-magnified view; **b** magnified view (× 20; indigo carmine 0·2 per cent stain); **c** magnified view (× 60); **d** histological specimen showing tubular adenoma

Non-polypoid carcinoma

It has recently been hypothesized that the remaining third of CRCs derives from a discrete and independent non-adenomatous histogenesis or '*de novo*' pathway[13–17]. Indeed, a series of small carcinomas without evidence of concomitant adenomatous tissue was described in the western literature as early as 1962. A retrospective German review identified 155 small carcinomas without evidence of adenomatous tissue in 1995 – the first in western Europe[18]. Bedenne *et al.*[19] proposed the existence of two distinct types of CRC in 1992: an exophytic type accounting for 60 per cent of cases and arising from the adenoma–carcinoma sequence, and an ulcero-infiltrating type accounting for 40 per cent, developing *de novo*.

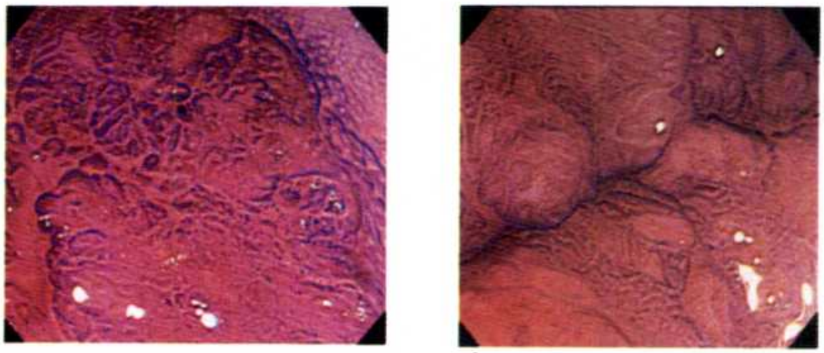
The flat adenoma–carcinoma concept

A suggested explanation for the origin of the ulcero-infiltrating type of CRC is that it derives from 'flat' or 'depressed' rather than polypoid lesions[20]. Such lesions are well reported in the Japanese literature and were described initially by Kariya[1] in 1977 and later in a large cohort by Kudo *et al.*[2]. Muto *et al.*[20] noted the existence of the small flat adenoma in 1985. Their description of 33 such lesions outlines the essential endoscopic features: a flat or slightly elevated lesion, less than 1 cm in diameter, sometimes having a central depression and often 'reddish' in colour. Histologically, most flat adenomas have a tubular as opposed to a villous architecture. An alternative theory to



a Non-magnified

b Non-magnified (stained)



c Magnified × 80

d Magnified × 100

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Fig. 3 Kudo classification type IIIs: small rounded pits, smaller than normal pits and in a compact disposition. This pit pattern results from a straight and shortened crypt structure, without branches of adenomatous tissue. The pattern generally suggests severe dysplasia and, sometimes, adenocarcinoma *in situ*. Fujii classification: neoplastic, non-invasive pit pattern. **a** Non-magnified view; **b** non-magnified view (indigo carmine 0·2 per cent stain); **c** magnified view (× 80; crystal violet 0·05 per cent stain); **d** magnified view (× 100; crystal violet 0·05 per cent stain). **c, d** Type IIIs pit in peripheral field with accompanying type V (Va)

de novo mucosal pathogenesis is that the flat adenoma is merely the precursor of the more typical, diminutive, polypoid adenoma[21]. Matsumoto *et al.*[22,23], however, argue that the endoscopic and histological features of the flat adenoma make this unlikely. They draw an analogy to the diminutive adenomas found in patients with familial adenomatous polyposis that are convex and discoid, with a horizontal or radial pattern of growth. It has even been suggested that many of the lesions described as small flat carcinomas, or flat adenomas with foci of carcinoma, are not actually malignant, the supposed existence of these lesions being explained in most cases as errors in histological diagnosis. The data of Tada *et al.*[14], however, offer further confirmation that these lesions are invasive adenocarcinomas.

Flat adenomas in European cohorts

Phantom carcinoma or Akita disease was once considered a phenomenon unique to Japan, until Rembacken *et al.*[3] clearly demonstrated a similar incidence of flat adenoma in a large European series. Current data suggest that flat adenomas account for more than 30 per cent of all colorectal lesions and have a significantly higher malignant potential than polypoid lesions[24]. Despite their small size, they exhibit high-grade dysplasia in more than 40 per cent of cases. Muto *et al.*[20] suggest that the small flat adenoma has a malignant potential that is greater than expected in relation to its size. Other studies have confirmed the higher than expected proclivity for malignant degeneration of small flat adenomas[25–27].

Invasive potential of flat adenomas

A number of investigators have suggested that small flat carcinomas readily invade through the muscularis mucosa into the submucosa and are associated with an increased risk of early metastasis to lymph nodes compared to cancers with a polypoid pattern of growth. Tada *et al.*[14] found extensive submucosal invasion in the majority of flat carcinomas. In

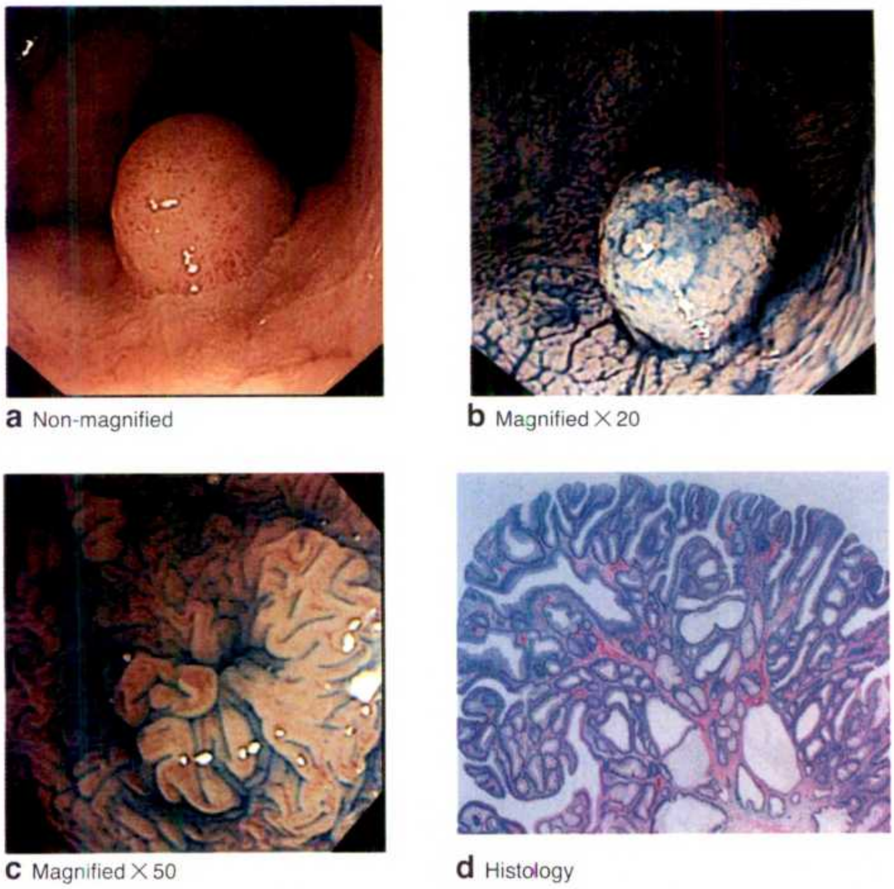
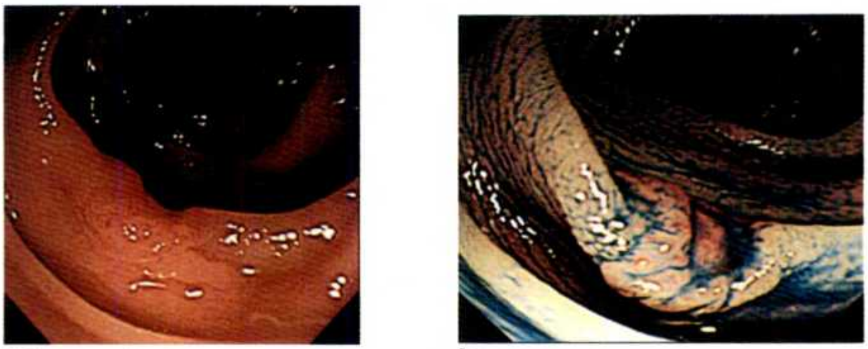


Fig. 4 Kudo classification type IV: large and tortuous pits, compared with the common adenomatous pits (IIIL), resembling a 'brain surface'. Generally this villous structure can be seen in conventional view and is found in large polypoid lesions and in laterally spreading tumours. Fujii classification: neoplastic, non-invasive pit pattern. **a** Non-magnified view; **b** magnified view (× 20; indigo carmine 0·2 per cent stain); **c** magnified view (× 50); **d** histological specimen showing tubulovillous adenoma

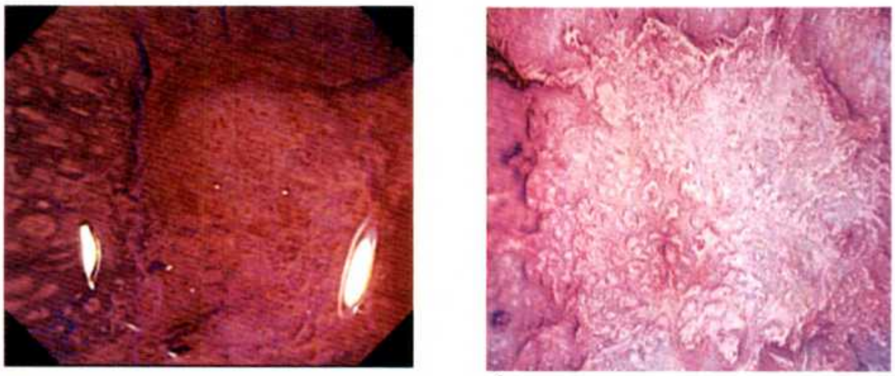
the study of Shimoda *et al.*[21] only 35 per cent of sessile and broad-based early polypoid carcinomas invaded the submucosa, whereas submucosal invasion was associated with 69 per cent of non-polypoid early carcinomas. Furthermore, the rate of lymphatic and venous invasion for polypoid carcinomas was only 32 per cent, compared with 77 per cent for non-polypoid carcinomas; the former accounted for only 22 per cent of 853 advanced colorectal carcinomas infiltrating the muscularis propria and deeper tissue, whereas the latter accounted for 78 per cent of malignancies invading the deeper tissue. The polypoid carcinomas were larger (mean 55 mm) than the non-polypoid tumours (mean 43 mm). In the study of Matsumoto *et al.*[23] non-polypoid tumours were smaller than polypoid cancers (median 9·5 *versus* 14·5 mm), but submucosal invasion was commoner for non-polypoid lesions (88 *versus* 9 per cent; $P = 0{\cdot}032$). Similar data have been reported in other studies[28–31]. Tada *et al.*[14] found nodal metastases associated with two of 12 lesions (both larger than 2 cm in diameter). Nodal metastases were found from three flat lesions less than 10 mm in diameter in the study of Minamoto *et al.*[28].

Early morphological changes in colorectal carcinoma – aberrant crypt foci

One of the earliest events in colorectal carcinogenesis is the alteration of the proliferation of epithelial cells in colonic crypts[11]. There is evidence of apoptotic malfunction and abnormal cell kinetics[32]. However, the early morphological features of colorectal tumour formation are not well defined. Most data describing the early visible changes of CRC are derived from experimental carcinogenesis and human pathological studies. Histological change in nor-



a Non-magnified **b** Magnified × 20



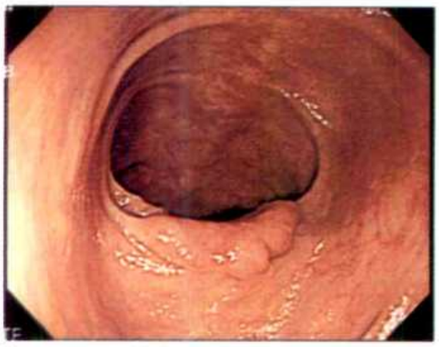
c Magnified × 80 **d** Magnified × 100

Fig. 5 Kudo classification type Va: pits with irregular shapes and variable size, configuring a heterogeneous morphology of pits. It is important to realize that, although the distribution is disrupted, all pits can be completely delineated. There is evidence that this pit pattern represents a superficially invasive carcinoma. Fujii classification: neoplastic, non-invasive pit pattern. **a** Non-magnified view; **b** magnified view (× 20; indigo carmine 0·2 per cent stain); **c** magnified view (× 80; crystal violet 0·05 per cent stain); **d** magnified view (× 100; crystal violet 0·05 per cent stain)

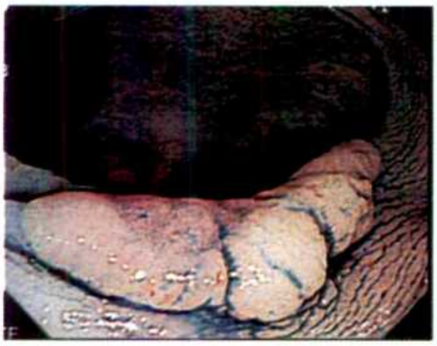
mal-appearing colonic mucosa remote from discrete colorectal neoplastic lesions has previously been observed both in animals treated with carcinogens[33] and in humans with colonic cancer[34]. In the mid-1980s, Bird[35] examined the methylene blue-stained mucosal surface of azoxymethane-treated mice under the light microscope (stereomicroscopy) and described crypts that appeared larger, thicker and darker than normal. They were described as aberrant crypts and considered to be possible precursors of (experimental) colonic cancer. Aggregate clusters of abnormal crypts were described and later classified as aberrant crypt foci (ACF)[36] which increase in size with time. Indeed, aberrant crypts undergo a replication process, as do normal crypts[37], which is initiated basally with budding and subsequent branching until two new crypts have been generated[38]. ACF have also been described in the human colon[39] where they are similar to those of rodents. Cell proliferation of flat colorectal mucosa is also altered in patients with colonic tumours and in those with a genetic or environmental risk of CRC[40].

Aberrant crypt foci and pit patterns in the human colon

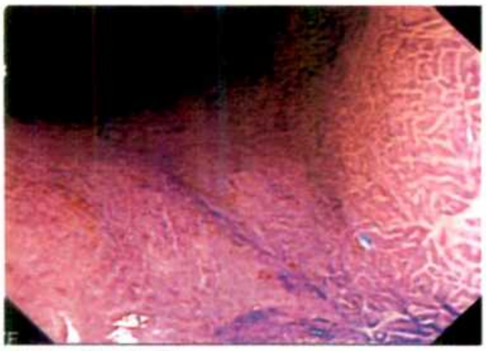
ACF in humans were first observed on the flat colonic mucosa of patients operated on for familial adenomatous polyposis, cancer or benign diseases of the large bowel[41]. Subsequently, such foci were observed on the unsectioned mucosa using stereomicroscopy[42]. Topologically, the lumens of aberrant crypts show various shapes, each predicting histological alterations[43]. The same features can be observed *in vivo* using a magnifying colonoscope[44]. Such observations now form the basis of pit pattern analysis at magnification chromoscopy *in vivo*.



a Non-magnified



b Magnified × 20



c Magnified × 100

Fig. 6 Kudo classification type Vn: when the pits cannot be completely traced or no pits can be found, the lesion is classified as Vn (non-structural). This finding suggests a deep invasion of the submucosal layer. Fujii classification: neoplastic, non-invasive pit pattern. **a** Non-magnified view; **b** magnified view (× 20; indigo carmine 0·2 per cent stain); **c** magnified view (× 100; crystal violet 0·05 per cent stain)

Pit pattern classification and magnification chromoscopic appearances

Assessment of the extent of a lesion by means of stereomicroscopy is a well established histopathological practice. Kosaka[45] first reported stereomicroscopic observation of the pit pattern in protruded lesions. Subsequently, Nishizawa *et al.*[46] reported stereomicroscopic findings of minute early superficial neoplasms, describing the absence of glandular orifices and non-structural pit patterns. Kudo *et al.*[2] later conducted stereomicroscopic observations of approximately 1600 lesions, creating the pit classification that is now well established in routine colonoscopic practice in Japan. Kudo[43] validated pit pattern classification by magnification video-chromoscopy in 1994, by showing a high correlation between *in vivo* magnification chromoscopy and *ex vivo* stereomicroscopy.

The Kudo classification describes five types of pit according to histological, macroscopic morphology and size (*Fig. 1*). Pit types I and II are restricted to benign hyperplastic and inflammatory mucosal polyps (i.e. non-tumours). Types IIIs, IIIL, IV, Va and Vn occur in adenomatous and neoplastic tissue (*Figs 2–6*). Fujii *et al.* have recently proposed a clinical classification system for crypt pattern interpretation that is simple for the endoscopist to use[47]. Lesions are placed in three basic clinical groups: non-neoplastic, non-invasive and invasive. Kudo crypt group I/II constitutes non-neoplastic, non-invasive patterns. Group IIIL/IIIs/IV/Va represents neoplastic but non-invasive lesions. Group Vn represents neoplasia with accompanying invasive characteristics.

Procedure for performing magnification chromoendoscopy

Two stains are used in conjunction with magnification imaging: indigo carmine and crystal violet (gentian violet).

Indigo carmine

Indigo carmine is a blue stain that accentuates the lesion's contours, providing details of the border and shape (*Fig. 7*). This dye is not absorbed systemically and so is not toxic when applied directly to the colorectal mucosa. It is used as an aqueous solution at 0·2–2 per cent concentration (vol/vol) that is flushed through the biopsy channel at volumes of 3–5 ml with 15 ml of air. Before this dye spraying, however, a standard mucosal toilet is requested, with a flush of water to remove mucous secretion from the intended examination site; excess mucus attenuates the clarity of image obtained with the dye and impairs diagnostic sensitivity.

Crystal violet

Crystal violet is a reacting contrast medium. Although there are no known case reports from the Japanese literature describing adverse reactions when used in the setting of

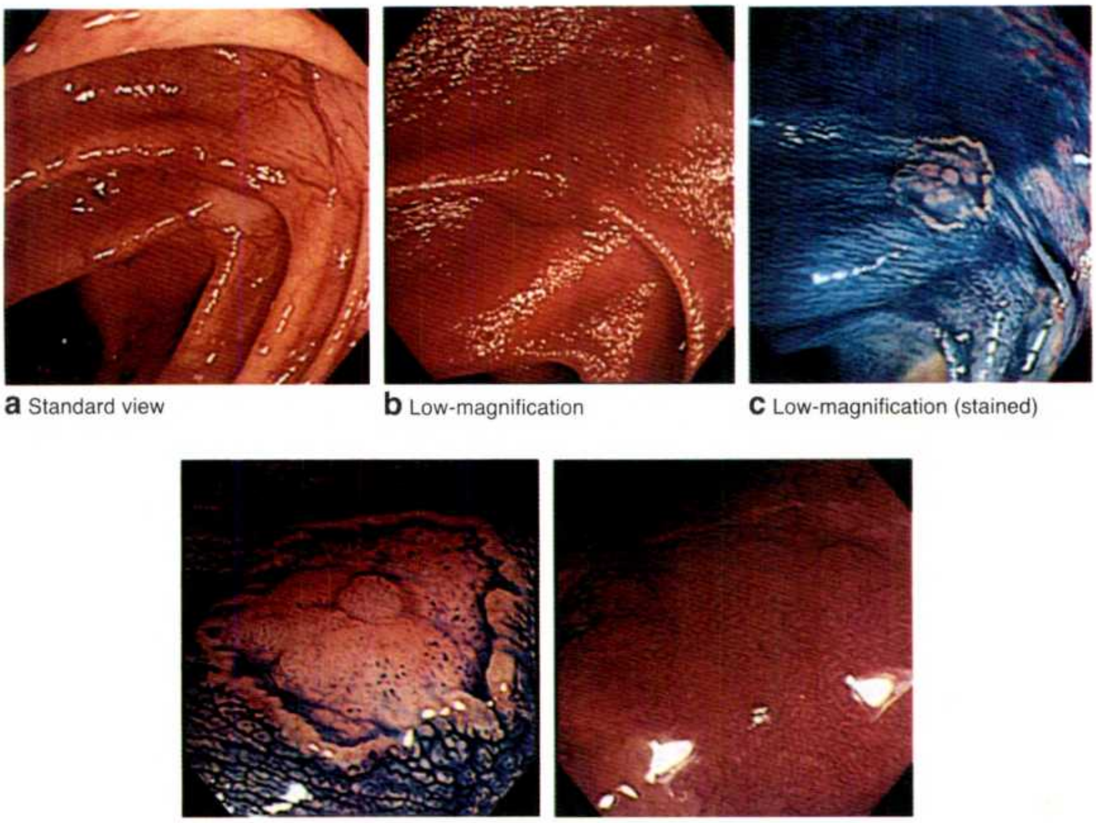

a Standard view
b Low-magnification
c Low-magnification (stained)
d High-magnification (× 80,stained)
e High-magnification (× 100,stained)

Fig. 7 Procedure for magnifying endoscopy; example of a hyperplastic polyp with flat elevation. **a** Standard colonoscopic view; **b** low-magnification view; **c** low-magnification view (indigo carmine 0·2 per cent stain); **d** high-magnification view (× 80; indigo carmine 0·2 per cent stain); **e** high-magnification view (× 100; crystal violet 0·05 per cent stain) (type II/IIIL pit pattern)

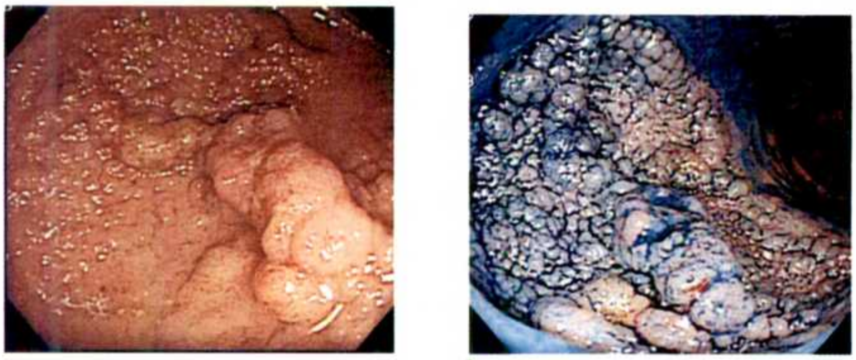
colonoscopy, there are *in vitro* and animal studies suggesting possible long-term toxicity[48]. The use of crystal violet should therefore be reserved for situations in which diagnostic precision will significantly influence management (e.g. differentiation of pit types Va and Vn). If the lesion demonstrates a non-destructive pit pattern, it is probable that the depth of invasion is limited to the mucosal or superficial submucosal layer; this is an indication for endoscopic mucosal resection. If a destructive pit pattern is found, the tumour is likely to have invaded the deep submucosal layer (at least), making surgical resection the management of choice.

When using crystal violet, the lesion is first washed with a proteinase solution (acetylcysteine 2 mg/ml) to remove all mucous secretion from its surface. Small drops of the dye at 0·05 per cent concentration (vol/vol) are applied to a clean mucosal surface with a specialized non-traumatic catheter (Olympus™ 6233064, Olympus Instruments, Tokyo, Japan). Excess dye is removed using the scope's lens cleaner. Some 2–3 min are necessary to allow optimal dye fixing, after which the magnifying view is performed. If the tumour is not in a good position for assessment, the non-traumatic catheter may be used to push and hold the surrounding mucosa to provide an improved position.

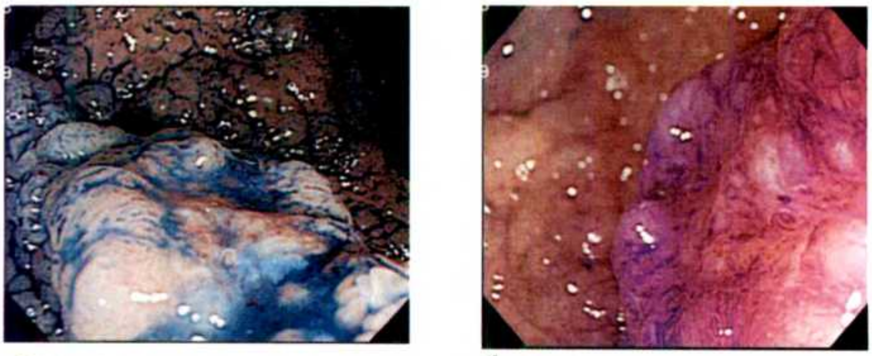
Magnification chromoscopy in routine clinical practice

Chromoendoscopy and magnification colonoscopy are potentially powerful tools in the detection of non-polypoid colorectal lesions. While the detection of large protruded lesions does not require chromoscopic enhancement, pit pattern appearances at the surface may help to predict neoplastic invasive depth (*Fig. 8*). The management of such lesions may therefore change, and involve guided biopsies and tattooing, or endoclip marking, for later surgical intervention.

Within Japanese colonoscopic practice, chromoscopy is generally used as an adjunct to basic non-enhanced endoscopic diagnostic techniques. However, the method



a Non-magnified **b** Non-magnified (stained)



c Magnified × 60 **d** Magnified × 100

Fig. 8 Example of deeply invasive carcinoma within a large nodule of a laterally spreading granular lesion. Type V (Vn) pit pattern clearly demonstrable at high magnification after crystal violet chromoscopy. Fujii classification: neoplastic, invasive pit pattern. **a** Colonic laterally spreading granular lesion; **b** non-magnified view (indigo carmine 0·2 per cent stain); **c** magnified view (× 60; indigo carmine 0·2 per cent stain); **d** magnified view (× 100; crystal violet 0·05 per cent stain) (type Vn pit pattern)

is used as a matter of routine at the National Cancer Centre, Tokyo, although pan-mucosal colonic chromoscopy is rarely carried out, except in the context of diagnosis and screening in cases of hereditary flat adenoma syndrome (HFAS) and hereditary non-polyposis colorectal carcinoma (HNPCC). The principal phenotypic marker in HFAS is multiple flat or plaque-like adenomas with a right hemi-colonic preponderance; HNPCC cases demonstrate high ACF density clusters and microadenoma formation[49–51]. All such lesions are more easily detected using magnification chromoendoscopy. However, the precise role of this new method in the detection, follow-up, screening and ultimate outcome of patients with the familial CRC syndromes awaits clarification.

Subtle endoscopic signs, such as mucosal erythema, paleness, haemorrhagic spots, absence of vascular network pattern, unevenness or mucosal deformity, may initially detect flat, depressed and superficial elevated types of colorectal lesion. Following such detection, magnification chromoscopy becomes a useful tool. Qualitative diagnosis of early cancer is often reflected by endoscopic features of marginal irregularity, 'star-shaped' depression, air-induced deformation (under altered air volume) and the absence of innominate grooves. Such endoscopic abnormalities should prompt localized dye spraying or chromoscopy to aid visualization of the lesion. Subsequent magnifying views can determine abnormal pit pattern structure, particularly pit types IIs and Vn, which may signify overt neoplastic change with deep invasive mucosal characteristics, now referred to as the Fujii invasive pattern. Alternatively, should a lesion be deemed suitable for endoscopic mucosal resection or another endoscopic resection technique, confirmation of the presence or absence of residual abnormal tissue can be checked easily by looking for a non-invasive pit pattern at the resection margin. Should resection appear incomplete, further endoscopic attempts may be made to resect residual tissue to a non-invasive margin (as dictated by pit morphology), or appropriate mucosal markings may be made (should surgery be required).

Conclusion

ACF are precursors of both experimental and human colonic cancer. Larger ACF, with altered morphology, dysplastic histological findings, altered cell kinetics and mutations in some genes involved in colorectal carcinogenesis, are the most probable candidates for progression to carcinoma. It is also evident that ACF have most of the requisites necessary for use as practical early biomarkers of cancer risk. This is so in both experimental and human intervention studies aimed at reducing the incidence of CRC. Magnification chromoscopy is therefore useful for the recognition of some of the earliest events of colonic carcinogenesis and in testing measures to prevent CRC. In the future, endoscopic identification of gross endoluminal pathology alone is likely to be regarded as inadequate. A basic working knowledge of chromoscopy and pit pattern interpretation may become a requirement for most in endoscopic practice; these techniques are already well established in Japan.

Acknowledgements

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Randomized clinical trial of screening for abdominal aortic aneurysm in women

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Background: Screening for abdominal aortic aneurysm (AAA) is commonly restricted to men. Recent studies have indicated a possible increase in deaths due to ruptured AAA in women, and a higher rate of rupture in women than in men. The present report details results from a randomized controlled trial that assessed the effects of screening women for AAA.

Methods: Some 9342 women aged 65–80 years were entered into the trial and randomized to age-matched screen and control groups. A single ultrasonographic scan was offered to women in the screening arm of the study. Women with an AAA received follow-up scans, and were considered for elective surgery if certain criteria were met.

Results: The prevalence of AAA was six times lower in women (1·3 per cent) than in men (7·6 per cent). Over 5- and 10-year follow-up intervals, the incidence of rupture was the same in the screened and control groups of women.

Conclusion: Screening women for AAA is neither clinically indicated nor economically viable.

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Introduction

The majority of studies evaluating abdominal aortic aneurysm (AAA) screening have chosen to screen men, concentrating on those over 60 years of age[1–7]. AAA prevalence is one factor in determining a population to screen, but incidence of rupture is another important consideration because the aim of screening is to prevent rupture, not just to detect those with an AAA.

It has been suggested that the mortality rate associated with ruptured AAA among women is increasing[8], and that the rate of rupture is higher in women than in men[9]. To assess the value of screening women for AAA, a screening programme was set up as part of a randomized controlled trial. The current report details results after 10 years of follow-up.

Patients and methods

A randomized controlled trial was set up in Chichester in 1988 to screen both men and women for AAA. A detailed description of the trial methods and patient group has been published previously[10]. Some 9342 women and 6433 men were recruited to the trial. They were aged 65–80 years and were identified from general practice lists and health authority lists.

The women were randomized into age-matched screening and control groups, comprising 4682 and 4660 women respectively. Women in the screening arm of the trial were invited by letter to attend for ultrasonographic measurement of the abdominal aorta; screening clinics were held at local hospitals and health centres. One reminder letter was sent if there was no response to the initial invitation. Patients in the control group were not contacted.

Women in whom an AAA was detected (aortic diameter 3 cm or greater) were followed with repeat ultrasonography at intervals depending on the diameter of the aneurysm. Surgical repair was considered if the aortic diameter measured 6 cm or greater, the diameter increased by 1 cm or more in a year, or the aneurysm became symptomatic. Death from rupture was identified using data obtained from the district Registrar of Births and Deaths.

Results

In an unselected general practice population of 4682 women, 3052 attended for screening. Age- and sex-related prevalence and mortality rates have been reported in detail for this trial elsewhere[10]. The prevalence of AAA in women was six times lower than that in men for all age groups; the

Table 1 Prevalence of abdominal aortic aneurysm (3 cm or more in diameter) by age and sex in screened men and women

	Percentage with AAA	
Age (years)	Men	Women
65	5·9	0·0
66–70	5·9	1·0
71–75	9·0	1·8
76–80	9·2	1·6
Total	7·6	1·3

AAA, abdominal aortic aneurysm

Table 2 Incidence of ruptured abdominal aortic aneurysm in control (*n* = 4660) and screened (*n* = 4682) groups of women, over 5- and 10-year intervals

	1989–1993	1989–1998
Control	3	9
Screened	3	10
Refused screening	1	4

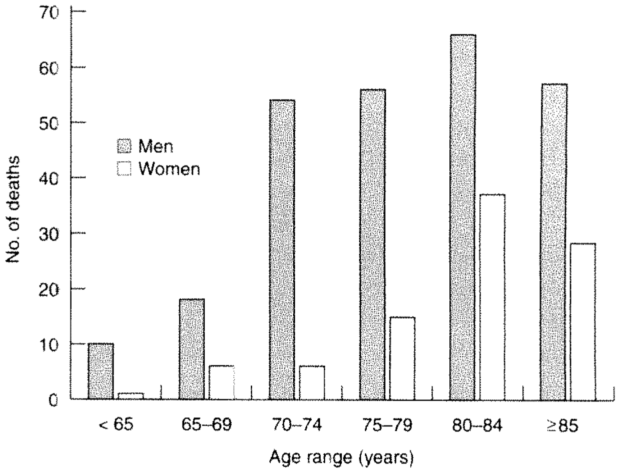

Fig. 1 Number of deaths from ruptured abdominal aortic aneurysm by age and sex in the entire Chichester area population excluding screened patients (166 000 people), 1989–1998

overall prevalence was 1·3 per cent in women compared with 7·6 per cent in men (*Table 1*).

None of the women in the screened group who had elective AAA repair died within 30 days of surgery. One woman in the control group died within 30 days of repair of a symptomatic AAA and was included in the number of deaths due to rupture. There were three ruptures in the control group between 1989 and 1993, rising to a total of nine overall between 1989 and 1998 (*Table 2*). Of the nine women, four had AAA repair and one survived.

There was no reduction in the number of ruptured AAAs over either the 5- or 10-year intervals in the screened group of women. Ten women from the screened group had AAA rupture or emergency repair, of whom four initially had a normal scan. Of the six with a detected AAA, one declined surgery, three declined further scans despite repeated invitations and died without surgery, one was judged unfit for elective repair and died within 30 days of emergency surgery, and one presented with symptoms after reaching the criteria for elective surgical repair (expansion of 1 cm or more in 1 year) and survived operation.

The number of deaths from AAA rupture in the unscreened local population is shown by age and sex in *Fig. 1*. More than half the deaths from ruptured AAA in men occurred before the age of 80 years; the majority of women (70 per cent) suffered AAA rupture after the age of 80 years.

Discussion

Most screening centres currently exclude women because of the low prevalence of AAA. Other factors relevant to this debate have been reported recently: the age of AAA onset and the increasing rate of rupture.

The AAA prevalence–age curve for women is shifted to the right (increasing age) by approximately 10 years compared with that for men. The female to male ratio of ruptured AAA increases with age, and the average age of a woman with a ruptured AAA is 6 years greater than that for a man[11]. Because of the later development of AAA, it could be argued that screening in women should be carried out at age 75 years. However, screening at age 75 years has implications for a patient's suitability for surgery and number of life years saved, owing to the greater co-morbidity.

A 14 per cent rise in mortality rate from ruptured AAA in women has been observed between 1989 and 1998[12,13], compared with a 4 per cent rise in men over the same interval. The number of elective and emergency AAA repairs increased over this interval, but mainly in men[8].

Other studies[11,14,15] have reported that women are less likely to have surgery for ruptured AAA. Reasons included increased age and associated co-morbidity at presentation, and reduced awareness of AAA in women.

The risk of AAA rupture is three times higher in women than in men, after correction for age, initial AAA size, body mass index and height[9]. This may reflect the prevailing treatment regimens. There may be a case for modifying the criteria for treatment of AAA according to gender; elective surgery might be considered on smaller aneurysms in women[9,11]. Further investigations into the incidence and natural history of AAA in women are needed.

The Chichester study demonstrated the low incidence of rupture in women aged under 75 years. In addition, it provided evidence that screening for AAA does not affect the incidence of rupture in women. Data collected from death certificates may be of limited reliability in determining mortality rate from ruptured AAA. However, if sudden death occurs in a patient who has either a known AAA or a reference in their records to aneurysm screening clinic attendence, AAA rupture is more likely to be recorded as the cause of death. Any bias is therefore likely to be against the benefit of screening.

The objective of any successful screening programme should be to enable intervention that conveys a clear clinical benefit to be appropriately targeted, whilst remaining cost effective. There is little benefit in knowing about the presence of an AAA in a subject who has a very low risk of ever developing symptoms or experiencing rupture. There may be a significant quality of life cost owing to the anxiety caused.

Ruptured AAA causes 0·8 per cent of all deaths in women aged 65 years or over, compared with 2·1 per cent of all deaths in men[16]. A major determining factor when considering routine screening of women must be whether it is economically viable. At present it would appear that it is not, owing to the low number of AAAs in women.

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Randomized clinical trial of no wound drains and early discharge in the treatment of women with breast cancer

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Background: Women undergoing surgery for primary breast cancer routinely have suction drains inserted deep to the wounds, which are removed approximately 6–8 days after operation, requiring a period of stay of that duration in hospital. The aim of this study was to perform a prospective randomized clinical trial to evaluate a new surgical technique of suturing flaps without wound drainage, combined with early discharge, in women undergoing surgery for breast cancer.

Methods: A total of 375 patients undergoing surgery for breast cancer were randomized to conventional surgery or suturing of flaps with no drain. The main outcome measures were length of hospital stay, surgical morbidity, psychological morbidity and health economics.

Results: Suturing of flaps and avoiding wound drainage in women undergoing surgery for breast cancer resulted in a significantly shorter hospital stay. Adopting this surgical technique with early discharge did not lead to any difference in surgical or psychological morbidity. Health economic benefits to the National Health Service resulted from saved bed days with no impact on community costs.

Conclusion: Wound drainage following surgery for breast cancer can be avoided, thereby facilitating early discharge with no associated increase in surgical or psychological morbidity.

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Introduction

Breast cancer remains the commonest malignancy in women, with 26 000 new cases diagnosed in the UK annually[1]. In the majority of women with breast cancer, excision of the primary tumour (by mastectomy or wide local excision) with axillary lymphadenectomy is standard surgical treatment. This facilitates tumour clearance and staging of disease. Following surgical excision, standard practice involves insertion of suction drains deep to mastectomy flaps and in the axilla, with the purpose of reducing seroma formation after operation[2]. Drains are left *in situ* until fluid drainage is less than 50 ml/day although this practice varies. As a result of this policy, the mean hospital stay is 6–8 days[3,4]. Despite the use of suction drains, seromas requiring aspiration still occur in 10–52 per cent of patients following drain removal[5].

In the light of increasing pressure for more efficient use of hospital beds, several studies have examined the feasibility of early discharge of patients with drains *in situ*[3,4,6]. An alternative surgical approach to facilitate early discharge has been described[7,8]. This consisted of suturing skin flaps to underlying muscle in an attempt to obliterate dead space and was combined with wound drainage. Suction drains were removed at 48 h and a significant reduction in the rate of postoperative seroma formation was noted. In a preliminary study, Jeffrey *et al.*[9] avoided drainage of the axilla in patients undergoing breast-conserving surgery. Ultrasonography demonstrated development of seroma in 92 per cent of patients, with only half of these requiring aspiration.

A pilot study of suturing flaps and avoiding wound drains was initially performed in 30 patients undergoing mastect-

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The Editors have satisfied themselves that all authors have contributed significantly to this publication

omy and axillary clearance. Seromas were detected in 90 per cent radiologically and 60 per cent clinically, with only half of these requiring aspiration for symptoms of discomfort[10]. Therefore, a prospective randomized trial was planned to evaluate this surgical approach as a means of facilitating early discharge in women undergoing surgery for breast cancer. It was conceivable that this surgical technique might impair shoulder movement and have some impact on overall psychological morbidity owing to early discharge home. It was therefore considered important to evaluate the physical, psychological and health economic issues.

Patients and methods

Protocol

The study was designed as two parallel randomized trials following the same protocol, one for women undergoing breast-conserving surgery and one for women undergoing mastectomy. It was planned for each of the two trials to enrol a total of 200 women over 2 years, randomized in equal numbers to receive a wound drain or not. This sample size was chosen to allow a definitive assessment of psychological morbidity, based on data reported by McArdle *et al.*[11]. This relatively demanding endpoint in terms of statistical power meant that the sample size was comfortably adequate for comparing the primary endpoint of length of hospital stay. It was recognized that comparing the two main randomized groups of drain *versus* no drain would only allow the detection of substantial differences in surgical morbidity. For example, there would be 80 per cent power to detect a 30 per cent complication rate being reduced to 15 per cent at the 5 per cent significance level.

Patients undergoing surgery for primary breast cancer were considered eligible for inclusion in the study. Pregnant women, patients deemed unsuitable for early discharge home owing to extreme anxiety or poor social support, or patients with any serious underlying medical condition that precluded full study participation were excluded from the study.

Approval was granted by the local research ethics committee. Following informed written consent, patients were randomized to receive a wound drain or not using consecutively numbered opaque envelopes. This was a single-centre trial and no stratification was used (other than different randomization schedules for the two trials). The randomization used randomly chosen block sizes of four and six to maintain balance without compromising the blinding of treatment assignment in this open study.

The randomization arms of the study were as follows. Patients undergoing mastectomy had level 2 axillary clearance combined with conventional wound drainage and discharge home on drain removal (control group) or level 2 axillary clearance, combined with suturing of flaps, no drains and early discharge from hospital (study group). Patients undergoing wide local excision had level 2 axillary clearance combined with conventional wound drainage and discharge home on drain removal (control group) or level 2 axillary clearance with suturing of flaps, no drains and early discharge home (study group).

Patients randomized to the control arm of the study had wounds drained by Portovac® drains (Howmedica, London, UK). A single drain was placed in the axilla in all patients and a second drain under the mastectomy flaps. The breast cavity was not drained after wide local excision. Drains were removed when the volume of drainage fluid was less than 50 ml over 24 h or at 5 days after operation, whichever occurred first. In patients randomized to no drainage the flaps were sutured to the underlying pectoralis major (mastectomy) and serratus anterior muscles (axillary clearance) with multiple parallel rows of 3/0 undyed Vicryl® sutures (Ethicon, Edinburgh, UK). These sutures were inserted commencing at the apex of the axilla and the cephalic aspect of the upper flap. Care was taken to avoid inclusion of the nerve to serratus anterior which can be vulnerable. No sutures were inserted in the cavity of the breast following wide local excision. Skin closure was performed using 3/0 PDS® (Ethicon).

Primary outcome measure

The primary outcome measure was length of hospital stay. Patients in the control arm were discharged home after drain removal. Patients in the study arm were discharged within 48 h if they were fully mobile, able to perform common activities of daily living, able to tolerate a full diet, required only oral analgesia and affirmed that they could manage at home.

Secondary outcome measures

Surgical morbidity

All wounds were assessed clinically on a daily basis until discharge, at the first postoperative visit, and at 1 and 3 months. All clinical seromas that caused discomfort were aspirated. The volume and number of aspirations was noted. Signs of wound infection were recorded using a standard grading system, the ASEPSIS score[12]. This is a well validated method of scoring wound infection based on wound characteristics, bacteriological assay and need for antibiotic therapy. Based on a scoring system, a score of more than 10 was taken as a cut-off for established wound infection.

Information leaflets regarding shoulder exercise were given to all patients before operation. Patients were visited by a physiotherapist on the day after operation for assessment of their mobility and supervised commencement of exercises. It was envisaged that suturing of flaps to underlying muscle might interfere with shoulder mobility in the short term, leading to longer-term shoulder morbidity. The range of shoulder movement was assessed before operation, at the first postoperative visit and after 1, 3 and 12 months. The degrees of flexion, abduction, and internal and external rotation were measured using a goniometer.

Psychological morbidity

Psychological measures were chosen that permitted assessment of patients' distress, coping, adjustment and beliefs, and personality, all of which are relevant to the diagnosis and treatment of breast cancer[13–18]. The General Health Questionnaire (GHQ-28)[19] has well established norms to define clinical levels of psychological distress. The Mental Adjustment to Cancer (MAC) scale[20] assesses styles of coping with malignant disease which predict adjustment and affective state[21,22]. The Illness Perception Questionnaire (IPQ)[23] assesses patients' cognition and perception about their disease and its anticipated effects on their psychosocial functioning. The Eysenck Personality Scales (EPS)[24] provide a broad measure of personality, in particular, extroversion and neuroticism, the latter being a predictor of poor adjustment and outcome across a wide range of medical conditions and treatment[25,26].

At the time of discharge, patients were given the EPS, GHQ-28, IPQ and MAC questionnaires with instructions to complete and return them at the first postoperative visit. Subsequently questionnaires were sent to patients at 3, 6 and 12 months (apart from the EPS which assesses stable personality characteristics and was therefore administered once only).

Health economics

The aim was to estimate costs to both the National Health Service (NHS) and patients. Health services resource use was estimated using standardized data collection forms, medical records, diaries completed by patients and questionnaires. A research nurse recorded the length of operation and the number of consumables (drains and sutures) used by each patient in theatre using a standardized data collection form. Data was also extracted on postoperative length of stay in hospital from medical records. Patient diaries were used to record contacts with primary or secondary care services in the 3 months following discharge from hospital. Self-completed questionnaires were used to estimate costs to patients and their families in terms of actual out-of-pocket expenses and disruption to normal activities. Where cost data are reported, 1999 prices were used (£Sterling).

Statistical analysis

Analysis was performed on an intention-to-treat basis. The data are summarized using mean(s.d.) for baseline characteristics and mean(s.e.m.) for postoperative assessments. The formal analysis of length of stay was based on two-sample t tests with corresponding 95 per cent confidence intervals (c.i.). The data on shoulder abduction are presented for each assessment, but the formal analysis is based on calculating a single summary measure for each patient, namely the mean of the postoperative 3-, 6- and 12-month assessments[27]. The mean of this summary measure was compared between the randomized groups using analysis of covariance (ANCOVA), with a baseline measurement as a covariant.

The mean GHQ total score at 12 months was compared between groups using ANCOVA with the extraversion and neuroticism scores as covariates. The present study was concerned with overall differences in physical and psychological outcome between the procedures, and the GHQ provided the measure of psychological distress. The other psychological assessments, while providing insight into patients' coping and beliefs about their illness as a function of the procedure, showed no evidence of a difference and are not considered further.

Results

Patient entry into the trial is demonstrated in the consort flow chart (*Fig. 1*). Overall, 18 patients randomized to the study arm had wound drainage because of surgical intraoperative oozing. The baseline characteristics of patients in the different groups were similar for age, EPS and shoulder movement (*Table 1*).

Length of stay

In the mastectomy trial the length of stay in the no drain group was reduced by a mean of 1·41 (95 per cent c.i. 1·04 to 1·78) days (t = 7·5, 188 d.f., $P < 0{\cdot}001$); the corresponding figure for the wide local excision trial was 1·55 (95 per cent c.i. 1·24 to 1·86) days (t = 9·9, 183 d.f., $P < 0{\cdot}001$).

Surgical morbidity

There was no evidence of a difference in seroma rates, volume of seroma fluid aspirated or wound sepsis (*Table 2*). In the mastectomy trial there was a mean overall difference

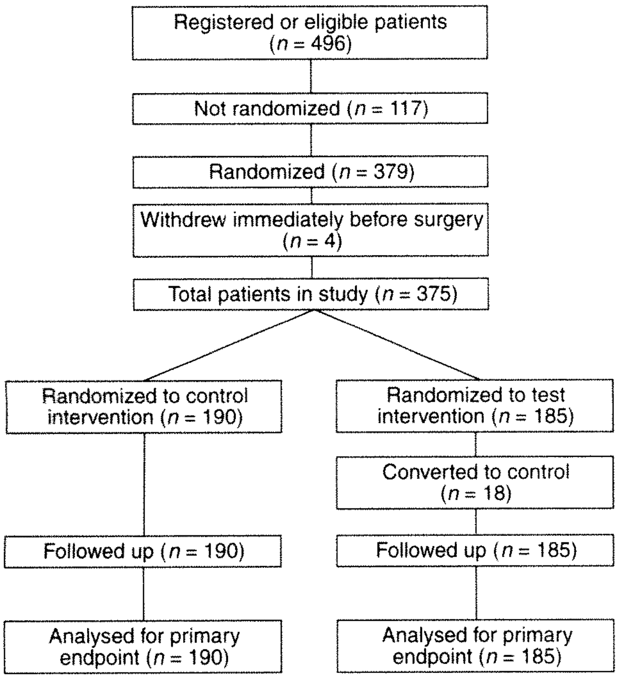
Registered or eligible patients
(n = 496)
Not randomized (n = 117)
Randomized (n = 379)
Withdrew immediately before surgery
(n = 4)
Total patients in study (n = 375)
Randomized to control intervention (n = 190)
Randomized to test intervention (n = 185)
Converted to control
(n = 18)
Followed up (n = 190)
Followed up (n = 185)
Analysed for primary endpoint (n = 190)
Analysed for primary endpoint (n = 185)

Fig. 1 Consort flow chart

in shoulder abduction of 2·4 (95 per cent c.i. – 0·8 to 6·1)° in favour of the drain group although this difference was not statistically significant (t = 1·51, 182 d.f., P = 0·13). The corresponding figure for the wide local excision trial was a non-significant mean overall difference of 0·7 (95 per cent c.i. –2·1 to 3·6)° in favour of the drain group (t = 0·52, 181 d.f., P = 0·61). Following an initial deterioration in shoulder mobility, all patients returned to near-normal shoulder function by 12 months (*Fig. 2*, *Table 2*). An identical pattern was observed with flexion, and internal and external rotation.

Psychological morbidity

In the mastectomy trial there was a mean difference of 1·2 (95 per cent c.i. – 0·5 to 2·9) GHQ points in favour of the drain group although this difference was not statistically significant (t = 1·39, 126 d.f., P = 0·17). The corresponding result for the wide local excision trial was a non-significant mean difference of 0·8 (95 per cent c.i. – 0·9 to 2·4) points in favour of the no drain group (t = 0·92, 127 d.f., P = 0·36). Neuroticism was a significant predictor of GHQ distress

Table 1 Baseline characteristics

	Mastectomy		Wide local excision	
	Drain	No drain	Drain	No drain
Sample size	96	94	94	91
Age (years)	58·1(12·1)	58·4(12·2)	57·1(9·1)	56·9(10·2)
Abduction (°)	172·4(16·6)	170·9(24·9)	176·6(11·0)	173·9(17·1)
Eysenck Personality Scales				
P-score	1·66(2·01)	1·83(1·60)	1·70(2·13)	1·40(1·18)
E-score	7·00(3·40)	6·19(3·27)	6·43(3·21)	6·67(3·65)
N-score	4·77(3·45)	5·42(3·46)	5·21(3·39)	5·23(3·41)
L-score	6·07(3·18)	5·56(3·15)	6·07(3·07)	5·88(2·97)

Values are mean(s.d.). P, psychotic; E, extraversion; N, neuroticism; L, lie

Table 2 Surgical outcomes

	Mastectomy		Wide local excision	
	Drain	No drain	Drain	No drain
Length of stay (days)*	5·59(1·05, 0·11)	4·18(1·51, 0·16)	4·86(1·16, 0·12)	3·31(0·96, 0·10)
Wound infection‡§	10 (10)	10 (11)	9 (10)	16 (18)
Seroma formation‡	52 (55)	57 (61)	46 (51)	41 (47)
Seroma volume (ml)†	213(41)	184(28)	122(24)	166(19)
Abduction, change from baseline (°)†				
After operation	– 27·9(2·6)	– 29·3(2·1)	– 23·0(2·0)	– 24·4(2.3)
3 months	– 6·9(2·0)	– 9·6(2·3)	– 10·7(1·9)	– 6·4(2·3)
6 months	– 2·8(1·9)	– 8·8(2·1)	– 5·5(1·5)	– 3·8(2·0)
12 months	– 0·1(2·3)	– 3·2(2·4)	– 2·2(1·8)	– 0·3(1·7)

Values are *mean(s.d., s.e.m.) or †mean(s.e.m.); ‡values in parentheses are percentages. §ASEPSIS score > 10

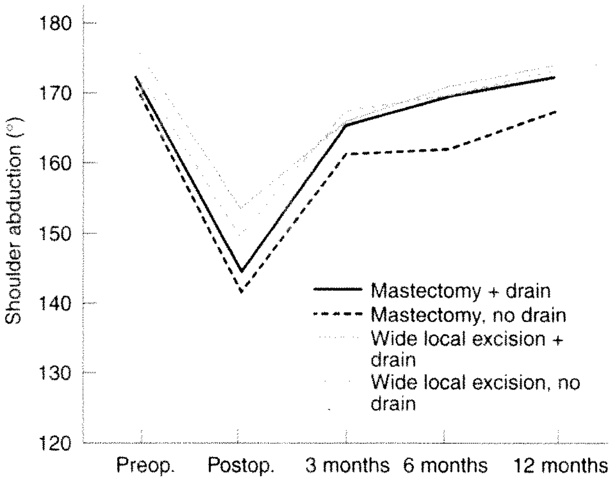

Fig. 2 Degrees of shoulder abduction

Table 3 General Health Questionnaire results, showing number of patients scoring above the cut-off indicating significant distress

	Mastectomy		Wide local excision	
	Drain	No drain	Drain	No drain
After operation	31 (38)	30 (39)	34 (43)	30 (38)
3 months	27 (39)	30 (42)	27 (40)	29 (39)
6 months	18 (25)	21 (33)	21 (31)	15 (22)
12 months	12 (17)	20 (30)	15 (22)	11 (16)

Values in parentheses are percentages

($P < 0{\cdot}001$) but did not differ as a function of treatment group. The percentage of patients whose scores exceeded the norm-defined criterion for 'caseness' (indicating clinically significant distress) was virtually identical across the four groups after operation and at 3-month follow-up (*Table 3*). Distress then generally declined to the 12-month follow-up, although a relatively higher percentage of patients who had mastectomy without drainage were reporting caseness at the final follow-up.

Health economics

Data on length of operation, consumables used in theatre and postoperative length of stay in hospital were available for 375 patients. There was no significant difference in the length of operation between patients who did or did not have a drain (66 *versus* 69 min; $P = 0{\cdot}11$). The latter patients overall had a significantly shorter length of stay in hospital (5·23 *versus* 3·75 days; $P < 0{\cdot}001$). The costs of consumables used in theatre were lower for patients with no drain, although this difference was small (£15·86 *versus* £13·08). Analysis of resource in primary and secondary care in the 3-month period following surgery showed no difference in general practitioner or district nurse visits, or contact with a breast care nurse or hospital ward and outpatient department. Pattern of costs to patients and families in terms of actual out-of-pocket expenses and disruption to normal activity were similar in both groups of patients.

Discussion

This study investigated the hypothesis that wound drainage following surgery for breast cancer could be avoided by suturing flaps to the underlying chest wall, thereby facilitating early discharge with no associated increase in surgical or psychological morbidity.

A decision was made not to discuss trial participation with some patients on the basis of advice obtained from the breast care nurses. It was felt that given the patients' anxiety or lack of adequate support at home, it would be inappropriate to broach the trial with these patients. The primary reason for patient refusal to enter the trial was related to uncertainty about early discharge home and concerns about coping. In all, 10 per cent of patients who were randomized to the study arm had drains inserted after surgical excision owing to intraoperative oozing. This technique is therefore feasible in the majority of patients with breast cancer.

Previous studies have examined the feasibility of early discharge of patients with either drains *in situ*[3,4,6] or early removal of drains at 48 h after operation following attempts at reducing 'dead space'[7,8]. The latter two studies adopted three rows of sutures to achieve this. In the present study, the technique of suturing flaps to underlying muscle was modified by introducing multiple parallel rows of sutures, thereby obliterating the dead space more effectively; this was combined with avoiding a wound drain altogether. While a reduction in seroma rate was noted in previous studies[7,8], this larger randomized study did not show any difference in rate of seroma formation. Although a higher incidence of infection was noted in patients who underwent wide local excision with no drainage, this was not statistically significant. Further investigation demonstrated that this was not related to the surgeon, operating theatre or a particular organism. Shoulder mobility demonstrated an initial reduction from baseline at the first postoperative visit to normal mobility at 3 months. The technique of suturing flaps therefore did not affect surgical morbidity.

Psychological morbidity was, perhaps understandably, relatively high in the 3 months after surgery, but did not vary significantly as a function of the procedure. Some 40 per cent of patients reported clinical levels of distress, a figure which contrasts with 26 per cent in random community samples[19]. The reduction in distress over the subsequent 9 months to around 20 per cent indicates a marked improvement in the psychological state of many patients. The relatively larger percentage of patients who were suffering distress at final follow-up after mastectomy without drainage would seem unlikely to be a consequence of the procedure, but may reflect some unrecognized bias in the allocation of patients to groups.

Early discharge as a consequence of avoiding wound drainage resulted in no difference in surgical or psychological morbidity. As shown in previous research, patients with neurotic traits suffered overall greater distress, which may have implications for subsequent psychological intervention. Furthermore, this policy has resulted in an overall reduction in cost to the NHS. This is a direct result of a shortened hospital stay with no increase in community costs following discharge home. The Department of Health has instituted waiting time initiatives, which have led to a significant pressure on hospital beds. Adoption of this surgical technique and policy of early discharge will be the sort of service change that will help ease some of this pressure.

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Randomized clinical trial of non-mesh *versus* mesh repair of primary inguinal hernia

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Background: The optimum method for inguinal hernia repair has not yet been determined. The recurrence rate for non-mesh methods varies between 0·2 and 33 per cent. The value of tension-free repair with prosthetic mesh remains to be confirmed. The aim of this study was to compare mesh and non-mesh suture repair of primary inguinal hernias with respect to clinical outcome, quality of life and cost in a multicentre randomized trial in general hospitals.

Methods: Between September 1993 and January 1996, all patients scheduled for repair of a unilateral primary inguinal hernia were randomized to non-mesh or mesh repair. The patients were followed up at 1 week and at 1, 6, 12, 18, 24 and 36 months. Clinical outcome, quality of life and costs were registered.

Results: Three hundred patients were randomized of whom 11 were excluded. Three-year recurrence rates differed significantly: 7 per cent for non-mesh repair ($n = 143$) and 1 per cent for mesh repair ($n = 146$) ($P = 0·009$). There were no differences in clinical variables, quality of life and costs.

Conclusion: Mesh repair of primary inguinal hernia repair is superior to non-mesh repair with regard to hernia recurrence and is cost-effective. Postoperative complications, pain and quality of life did not differ between groups.

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Introduction

Inguinal hernia repair is the most frequently performed operation in the Netherlands[1]. Consequently, failure of inguinal hernia repair not only affects individual patients but also has a great impact on society. Failure leads to increased patient discomfort, reoperations and sick-leave, and so may result in a considerable economic burden[2]. No consensus has yet been reached about the best surgical approach to inguinal hernia repair, which should show good cost-effective clinical results[3–5].

Recurrence rates after non-mesh suture repair of inguinal hernia vary between 0·2 and 33 per cent, depending on the surgical method, experience, length of follow-up and type of hospital[6–14]. Tension-free hernia repair, or repair with the use of mesh, was popularized by Lichtenstein and Schulman[15]. This method was associated with a lower recurrence rate than suture repair in a non-randomized study of primary inguinal hernia repair[16] and in two randomized studies[5,17].

The aim of this study was to establish the value of open mesh repair for primary inguinal hernia in the general hospital setting, not only with respect to clinical outcome but also quality of life and cost. A multicentre randomized trial with long-term follow-up was conducted.

Patients and methods

Between September 1993 and January 1996, patients older than 18 years scheduled for repair of a primary unilateral inguinal hernia were randomized to non-mesh or mesh repair. Patients could only be enrolled once and were not included if they suffered from bilateral inguinal hernia.

The Editors have satisfied themselves that all authors have contributed significantly to this publication

Patients were informed about the trial both verbally and in writing. Six hospitals participated in the study. Randomization was achieved by calling an independent randomization centre, where computer-generated lists were available, stratified by hospital. The protocol was approved by the ethics committees of all participating hospitals.

Age, obesity, intermittent high abdominal pressure (cough, constipation, prostatism) and factors that may interfere with wound healing (diabetes, use of steroid medication, smoking) were noted. Obesity was defined as a body mass index of 30 kg/m^2 or more. The type of inguinal hernia was also noted.

Evaluation of operation-related factors included surgical technique, type of anaesthesia, clinical setting or day care, and whether the operation was performed by a surgeon or by a surgical resident. Drainage, wound haematoma, seroma, wound dehiscence and wound infection were also recorded. Wound infection was defined as discharge of pus from the wound.

At the induction of anaesthesia, a single dose of intravenous broad-spectrum antibiotics was administered according to hospital protocol. Non-mesh repair was performed according to the surgeons' method of choice, provided that 2/0 polypropylene sutures (Prolene®; Ethicon, Johnson & Johnson, Somerville, New Jersey, USA) were used. Mesh repair was performed according to a strict protocol as described by Lichtenstein and Shulman[15] using a Prolene® or Marlex® (C. R. Bard, Billerica, Massachusetts, USA) polypropylene prosthetic mesh of 7·5 × 15 cm to avoid tension on the suture lines. The duration of surgery (from first incision to last skin suture), hospital stay and time off work were noted. Patients were followed up at 1 week and at 1, 6, 12, 18, 24 and 36 months. Awareness of hernia recurrence and complaints about the groin were noted and the groin was examined physically for recurrence of inguinal hernia. Hernia recurrence was defined as a bulge or weakness in the operative area exacerbated by a Valsalva manoeuvre and palpable outside the external ring. Hernia recurrence and death were the study endpoints. Patients who did not visit the outpatient department for follow-up at 36 months were asked to complete a questionnaire, and were visited at home by a physician who was not aware of the method used for inguinal hernia repair. If recurrences were found after follow-up had terminated, they were not included in the statistical analysis in accordance with the protocol.

To assess quality of life (or current health state) before and after surgery, the Dutch version of the EuroQol EQ-5D and the EuroQol Visual Analogue Scale (VAS)[18,19] was administered for self-completion by patients before operation and 1 week, 1 month and 6 months after operation.

To determine the cost-effectiveness of both methods of inguinal hernia repair, a questionnaire about costs was completed 1 and 6 months after surgery. This included questions about the need for help from a general practitioner, nurse or housekeeper, the need for pain medication and the duration of sick-leave. Cost-effectiveness also involved quality of life- and operation-related factors, such as duration of surgery, duration of hospital stay and time off work.

Statistical analysis was done with the Statistical Product and Service Solutions software (SPSS, Chicago, Illinois, USA). Percentages and continuous variables were compared using Fisher's exact test and Mann–Whitney *U* test respectively. Cumulative recurrence rates were calculated and compared using Kaplan–Meier curves and the log rank test. *P* values given are two sided; $P = 0{\cdot}05$ was considered the limit of significance. The primary analysis was by intention to treat. A univariate regression analysis for the non-mesh repair group was performed.

Results

Three hundred patients were randomized. Eleven patients were excluded. In four patients another type of hernia was demonstrated at operation. One patient needed bilateral repair. The operation was cancelled for three patients. In spite of inclusion in the trial two patients underwent laparoscopic inguinal hernia repair and one patient withdrew consent before operation. Preoperative characteristics were well matched between the two groups (*Table 1*). Eight patients (3 per cent) were women.

Table 1 Comparison of study groups

	Non-mesh repair group	Mesh repair group
Age (years)*	53 (19–85)	58 (24–83)
Body mass index (kg/m^2)*	25 (19–34)	25 (18–34)
Prostatism†	14 of 140	12 of 141
Constipation	11 of 143	10 of 146
Coughing	22 of 143	25 of 146
Diabetes	8 of 143	2 of 146
Use of steroids	2 of 143	4 of 146
Type of hernia		
Indirect	67	75
Direct	45	37
Combined	27	29
Not described	4	5

*Values are median (range). †Men only

Table 2 Cumulative recurrence rates 1–36 months of follow-up after primary inguinal hernia repair

Time after operation (months)	No. at risk for recurrence	Cumulative recurrence rate (%)
Non-mesh repair		
1	143	0
6	137	1(1)
12	131	1(1)
18	127	1(1)
24	125	3(2)
36	119	7(2)
Mesh repair		
1	146	0
6	138	0
12	138	0
18	133	0
24	131	0
36	122	1(1)

Values in parentheses are s.e.

Intention-to-treat analysis

Of the remaining 289 patients, 143 had been randomized to non-mesh repair and 146 to mesh repair. The type of inguinal hernia repair in the non-mesh repair group was Bassini–McVay in 75 patients (52 per cent), Shouldice in 36 (25 per cent), Bassini in 26 (18 per cent) and McVay in three (2 per cent). Three patients received a mesh because the surgeon decided at operation that a mesh repair was preferable. These procedures were marked as conversions. In the mesh repair group, 125 patients received a Prolene® mesh, whereas Marlex® was used in 13. On one occasion a resorbable polyglactin 910 mesh (Vicryl®; Ethicon, Johnson & Johnson) was used in error. Seven patients did not receive a mesh repair and these operations were marked as conversions.

Thirteen patients (4 per cent) died within the follow-up period from causes unrelated to inguinal hernia and more than 1 month after hernia repair. Follow-up was complete for 254 patients (88 per cent). Thirty-five patients (12 per cent) were lost to follow-up: 12 patients withdrew from follow-up, 12 patients could not be traced and 11 patients were followed up in writing at 36 months but were not physically examined at this time. All patients were included in the analysis with their follow-up censored at the time of last physical examination.

Recurrences

During the 3-year follow-up, nine recurrences were found in the non-mesh repair group and one in the mesh repair group. The only recurrence in the mesh group occurred in the patient who received a resorbable mesh in error. The 3-year cumulative recurrence rates in the non-mesh and mesh repair groups were 7 and 1 per cent respectively ($P = 0{\cdot}009$) (*Table 2*).

Exclusion of the patient who received a resorbable mesh from the analysis (major trial violation) decreased the 3-year cumulative recurrence rate from 1 per cent to zero, increasing the difference between groups ($P = 0{\cdot}002$). There were no recurrences after inguinal hernia operations that were converted peroperatively.

Univariate analysis

The non-mesh repair group was associated with a significantly higher recurrence rate. Risk factors were evaluated within this group. The recurrence rate was higher for older patients; 3-year recurrence rates for patients younger than 65 years of age and older patients were 3 and 16 per cent respectively ($P = 0{\cdot}01$). Other patient characteristics and wound complications were not identified as significant risk factors.

Operation-related factors

Median duration of surgery was 45 min for both non-mesh repair (range 19–105 min) and mesh repair (range 20–120 min). Seventy-nine per cent of patients were treated in a clinical setting and 21 per cent in day care; there was no difference between treatment groups. Median hospital stay was 2 days in both groups, with a range of 0–14 and 0–11 days respectively. Median time off work was 17 (range 0–56) days after non-mesh repair and 19 (range 2–113) days after mesh repair.

The type of anaesthesia did not differ between the groups (general 62 per cent, epidural 23 per cent, spinal 15 per cent). The type of hernia encountered at operation was comparable between the two groups (*Table 1*). In the non-mesh group, there was no recurrence of an indirect hernia, four recurrences of direct hernias and five recurrences of combined hernias. Surgeons and residents assisted by a surgeon operated on comparable numbers of patients (68 *versus* 78 and 78 *versus* 66 respectively). Of the ten patients with a recurrence, six were primarily treated by a surgeon and four by a resident (P not significant).

Complications

There was no significant difference between the non-mesh and mesh repair groups regarding postoperative wound infection (none of 143 *versus* one of 146; $P = 0{\cdot}32$), wound dehiscence (none of 143 *versus* one of 146; $P = 0{\cdot}32$), haematoma (17 of 143 *versus* 15 of 146; $P = 0{\cdot}66$) and

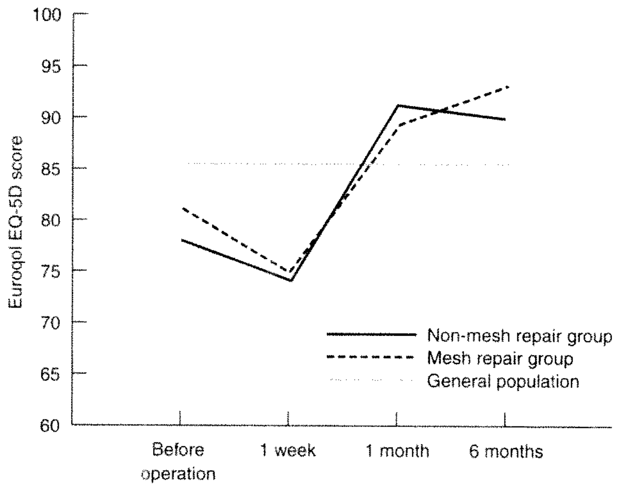

Fig. 1 Quality of life measured by Current Health State, EuroQol EQ-5D (minimum score 0, maximum score 100). Values are mean(s.e.m.). Number of respondents per timepoint ranges from 90 to 111 per treatment group

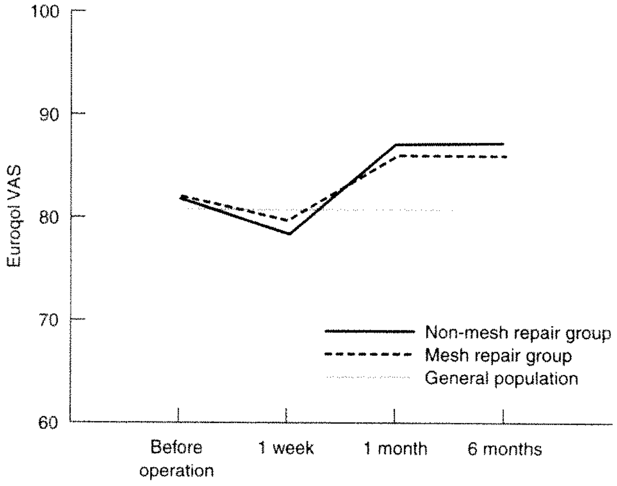

Fig. 2 Quality of life measured by the EuroQol Visual Analogue Scale (VAS) (minimum score 0, maximum score 100). Values are mean(s.e.m.). Number of respondents per timepoint ranges from 101 to 119 per treatment group

seroma (none of 143 *versus* four of 146; $P = 0{\cdot}62$). In the non-mesh group one patient suffered from urinary retention and one patient from pneumonia. Apart from recurrences, there were no long-term complications.

Postoperative pain (week 1: 45 of 140 *versus* 58 of 140 ($P = 0{\cdot}11$); 36 months: nine of 125 *versus* eight of 129 ($P = 0{\cdot}73$)) and discomfort (week 1: 78 of 140 *versus* 72 of 140 ($P = 0{\cdot}42$); 36 months: 13 of 125 *versus* 11 of 129 ($P = 0{\cdot}60$)) were similar at all timepoints.

Quality of life

The response rate for the Euroqol questionnaire and VAS ranged from 49 to 74 per cent for the non-mesh repair group and from 56 to 79 per cent in the mesh group, varying between timepoints. The quality of life did not differ significantly between groups at any timepoint. There were no significant differences between mean(s.d.) values for EuroQol EQ-5D or EuroQol VAS measured in the general population (85(8))[19] and 81(14)[20] respectively) and either study group (*Figs 1* and *2*).

Cost

The two groups paid a similar number of visits to the general practitioner (six of 143 and eight of 146 for non-mesh *versus* mesh repair) and required the assistance of a nurse or a housekeeper in a comparable number of cases (four of 143 *versus* two of 146). Use of analgesics was comparable (nine *versus* seven patients).

No difference was noted in operation-related factors and quality of life. Cost-effectiveness was therefore determined by the costs of polypropylene mesh (€53) and by the number of recurrences requiring reoperation. Repair of a recurrent inguinal hernia costs approximately €1600 in a Dutch hospital, including the specialists' fees, use of the operating room and a hospital stay of 2 days. To prevent the nine recurrences in the non-mesh group from developing, 143 meshes should have been used in hernia repair in this group, resulting in additional operating costs of €7579 for the whole group. At least €6821 would have been saved if mesh had been used for all repairs.

Discussion

Inguinal hernia repair performed by suturing and displacement of anatomic structures may lead to excessive tension on the suture line and surrounding tissue. Subsequently, tissue ischaemia and suture cut-out may occur, resulting in recurrence. The use of prosthetic mesh allows tension-free repair of inguinal hernia and, in theory, better results. The current series proves the superiority of this method over non-mesh repair in the long term with regard to hernia recurrence; in addition, there was no increase in cost, complications or postoperative pain and quality of life was comparable.

The incidence of complications did not differ significantly between groups, similar to the results of other randomized trials comparing mesh and non-mesh repair[4,5,17,21]. The reluctance of surgeons to use polypropylene mesh because of an assumed increase in the incidence of postoperative complications is thus unjustified. Postoperative pain and discomfort, duration of surgery, hospital stay and time off work were comparable in the two groups, as has been shown previously[4,5,17,21], although Barth *et al.*[4] reported a significantly longer duration of surgery in the non-mesh repair group and Prior *et al.*[21] described significantly less postoperative pain in the mesh group.

Quality of life evaluation showed no differences between the two operative groups, and thus was only determined by the number of recurrences after inguinal hernia repair. The additional cost of mesh for mesh repair was less than the cost of operating on recurrences, confirming that mesh inguinal hernia repair is a cost-effective method.

In conclusion, mesh inguinal hernia repair was associated with a lower recurrence rate than non-mesh repair; indeed, a recurrence rate of zero is within reach. No differences were found in complication rate, postoperative pain and quality of life, and mesh repair proved to be cost-effective. Therefore, mesh repair is the method of choice for primary inguinal hernia repair.

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Dynamic nature of early organ dysfunction determines outcome in acute pancreatitis

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Background: All patients with organ dysfunction are currently classified as having severe acute pancreatitis. The aim of this study was to characterize the systemic inflammatory response syndrome (SIRS) and early organ dysfunction in patients with acute pancreatitis and the relationship with overall mortality.

Methods: Patients with predicted severe acute pancreatitis of less than 48 h duration had daily organ dysfunction scores and SIRS criteria calculated. These features were then correlated with outcome.

Results: Of 121 patients, 68 (56 per cent) did not develop organ dysfunction; only two of these patients died (mortality rate 3 per cent). Fifty-three (44 per cent) had early organ dysfunction, of whom 11 died (21 per cent). Organ dysfunction and persistent SIRS were both associated with an increased mortality rate, but on multivariate analysis only deteriorating organ dysfunction was an independent determinant of survival.

Conclusion: Early organ dysfunction in acute pancreatitis usually resolves and in itself has no significant influence on mortality. In contrast, worsening organ dysfunction was associated with death in more than half of the patients (11 of 20); it is this group of patients who should be classified as having severe acute pancreatitis.

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Introduction

Death from acute pancreatitis occurs either early, within the first week, or later, in the second or subsequent weeks[1–3]. In either situation, the common mode of death is multiple organ dysfunction syndrome (MODS)[4].

Early MODS in the first week is a major cause of death in patients with acute pancreatitis. An audit of all patients (n = 13 727) in Scotland from 1984 to 1995 found that 54 per cent of deaths occurred during the first week[3]. While this is in agreement with an autopsy series[5] and other prospective studies[6–9], some reports describe infected pancreatic necrosis, which normally features later in the second or third week, as the major cause of death[10]. Early MODS also represents the most important non-fatal complication of acute pancreatitis, causing major morbidity and a strain on resources[4,11].

The clinically based classification system of acute pancreatitis (Atlanta criteria) therefore includes organ dysfunction in the definition of severe acute pancreatitis[12]. This classification regards organ dysfunction as an event that is either present or absent. Although it is well known that mortality rate increases with the number of failing organ systems[13], death is also related to the degree of dysfunction within an organ system[14]. Thus organ dysfunction is better described as a continuum of severity, using a numerical scale, such as an organ failure score[15,16]. Uniform definitions for the systemic inflammatory response syndrome (SIRS) and MODS have been accepted, stressing that organ dysfunction is a dynamic, reversible process[17,18]. These improvements in definitions have led to studies characterizing the clinical course of SIRS and MODS in a variety of conditions[16,19,20] other than acute pancreatitis.

The aim of this study was to describe the dynamic nature of early organ dysfunction and SIRS in patients with acute pancreatitis and to monitor how these affected survival.

Patients and methods

Some 121 patients who had taken part in a randomized clinical trial within the unit from 1997 to 1999 were included in the study. Patients with clinical and biochemical evidence of acute pancreatitis (serum amylase level more than three times the upper limit of normal) were recruited from 11 hospitals in the west of Scotland. Prospectively collected data were entered into a computerized database. To study early organ failure, patients were included if admitted within 48 h of onset of symptoms and if they had an admission Acute Physiology And Chronic Health Evaluation (APACHE) II[21] score of 6 or more, to select patients with more severe disease[22]. Patients with chronic or recurrent pancreatitis were excluded. During this interval 567 patients with acute pancreatitis were screened for inclusion; only 121 (21 per cent) fulfilled the criteria for predicted severe acute pancreatitis.

For each patient the following demographic and clinical data were recorded after informed consent had been obtained: age, sex, Glasgow Prognostic Index, aetiology and time from onset of symptoms to admission. To quantify organ dysfunction, a modification of a multiple organ failure score, as proposed by Bernard *et al.*[23], was used (*Table 1*). This scoring system was chosen because a score of two or more in any organ system approximated closely to the definitions of organ dysfunction laid down by the Atlanta criteria[12]. The parameters used were specific, easily obtained, and generally independent of therapy. Liver failure was not included in the modification of the Bernard scoring system as serum bilirubin level may be raised in many patients with gallstone pancreatitis without evidence of liver failure.

SIRS was defined by two or more of the following criteria[18]: pulse rate greater than 90 per min; respiratory rate above 20 per min or an arterial partial pressure of carbon dioxide ($P\text{aCO}_2$) of less than 32 mmHg; temperature higher than 38°C or less than 36°C; white cell count greater than 12 000 or less than 4000 cells/mm^3.

Using the prospectively collected data, organ dysfunction and SIRS scores were calculated on admission and daily for the first week. The worst score in any 24-h interval was recorded. A MODS score of 2 or more in any single organ system defined organ dysfunction and therefore severe acute pancreatitis according to the Atlanta definition[12]. Once a patient fulfilled the definition of having organ dysfunction, the cumulative daily organ dysfunction score was followed for the first week. Any subsequent score higher than the score on the day of diagnosis of organ dysfunction categorized the patient as having deteriorating organ dysfunction. If the score remained the same or improved during the remainder of the first 7 days, the patient was classified as having resolving organ dysfunction.

Survival was analysed by means of the Kaplan–Meier method with the log rank test; $P < 0{\cdot}05$ was considered significant. A Cox proportional hazards analysis was used to assess independent predictive power. Minitab® (release 9·2) and the Statistical Package for the Social Sciences® (version 9·0) (SPSS, Chicago, Illinois, USA) statistical software packages were used throughout.

Results

The median age of the 121 patients with predicted severe acute pancreatitis was 66 (range 30–91) years; there were 60 men and 61 women. The cause of pancreatitis was gallstones in 79 patients (65 per cent), alcohol in 22 (18 per cent), following endoscopic retrograde cholangiopancreatography in four (3 per cent) and unknown in 16 (13 per cent). Patients presented at a median of 26 (range 1–48) h after the onset of symptoms. The median APACHE II score on

Table 1 Modified multiple organ failure score

	Score				
	0	1	2	3	4
Cardiovascular system (systolic blood pressure; mmHg)	> 90	< 90, fluid responsive	< 90, not fluid responsive	< 90, pH < 7·3	< 90, pH < 7·2
Respiratory ($F\text{iO}_2/P\text{O}_2$)	> 400	301–400	201–300	101–200	< 101
Glasgow Coma Score	15	13–14	10–12	6–9	< 6
Coagulation (platelet count; $\times 10^9$/l)	> 120	81–120	51–80	21–50	< 21
Renal (creatinine; µmol/l)	< 134	134–169	170–310	311–439	> 439

Modified from Bernard *et al.*[23], $F\text{iO}_2$, fraction of inspired oxygen; $P\text{O}_2$, partial pressure of oxygen admission was 11 (range 6–25) and the median Glasgow Prognostic Index was 3 (range 0–7).

Only 50 of the 121 patients underwent computed tomography, a median of 6 days after the onset of symptoms. Fifteen (30 per cent) of these 50 patients had necrosis of more than 30 per cent of the pancreatic volume; seven of them developed infected necrosis and underwent necrosectomy.

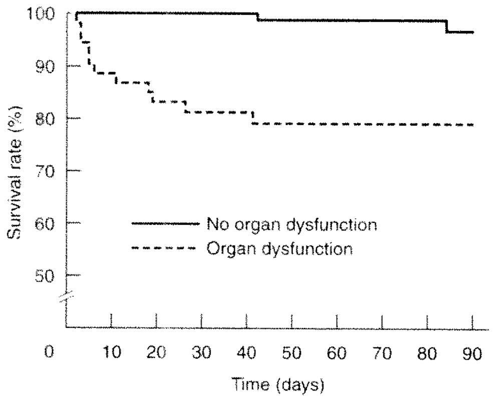
Overall, 13 of the 121 patients died (mortality rate 11 per cent). Sixty-eight (56 per cent) of the 121 patients did not develop organ dysfunction during the first week, a finding in keeping with the published description of APACHE II scoring in acute pancreatitis[22,24]. There were two deaths in this group (mortality rate 3 per cent), due to late septic complications. Both deaths occurred after 40 days of illness.

Early organ dysfunction complicated acute pancreatitis in 53 patients (44 per cent), of whom 11 died (mortality rate 21 per cent). The presence of early organ dysfunction was a significant determinant of survival; after 90 days, the survival rate was reduced from 97 to 79 per cent ($P = 0{\cdot}001$) (*Fig. 1*).

Of the 53 patients who had early organ dysfunction, 20 had deterioration of organ dysfunction during the first week; in the remaining 33 the organ dysfunction resolved. There were no deaths in patients whose organ dysfunction resolved, but 11 died of the 20 patients whose organ dysfunction deteriorated ($P < 0{\cdot}001$). Deteriorating organ dysfunction during the first week was a highly significant determinant of survival, with a reduction at 90 days from 98 to 45 per cent (*Fig. 2*). There were no deaths in patients who had early organ dysfunction that resolved.

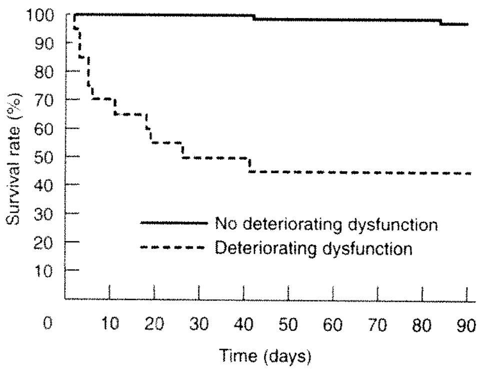
The presence or absence of SIRS on admission, at 24 h and 48 h as well as persistent SIRS (defined as SIRS present for the entire first 48 h) was correlated with survival (*Table 2*). The presence of SIRS at 48 h and also persistent SIRS correlated strongly with mortality. Of the 27 patients who had persistent SIRS, only 17 (63 per cent) survived, compared with 91 (97 per cent) of those who did not have persistent SIRS ($P < 0{\cdot}001$).

A Cox proportional hazards analysis was used to assess the independent predictive power of persistent SIRS and persistent organ dysfunction in determining survival. Only deteriorating organ dysfunction had independent predictive power ($P = 0{\cdot}001$). The hazard ratio of deteriorating organ dysfunction *versus* no deteriorating organ dysfunction was 41 (95 per cent confidence interval 9·1 to 188·7).



No. at risk										
No. dysfunction	68	68	68	68	68	67	67	67	67	66
Dysfunction	53	47	44	43	43	42	42	42	42	42

Fig. 1 Kaplan–Meier survival plot: effect of any organ dysfunction on survival in patients with severe acute pancreatitis. Early organ dysfunction was a significant determinant of survival. $P = 0{\cdot}001$ (log rank test)



No. at risk										
No. deterioration	101	101	101	101	101	100	100	100	100	99
Deterioration	20	14	11	10	10	9	9	9	9	9

Fig. 2 Kaplan–Meier survival plot: effect of deteriorating organ dysfunction on survival in patients with severe acute pancreatitis. $P < 0{\cdot}001$ (log rank test)

Table 2 Association between systemic inflammatory response syndrome and overall survival in patients with severe acute pancreatitis

	SIRS present		SIRS absent		
	n	Survivors	*n*	Survivors	*P**
Admission	87	74 (85)	34	34 (100)	0·019
24 h	45	35 (78)	76	73 (96)	0·002
48 h	32	21 (66)	89	87 (98)	< 0·001
Persistent	27	17 (63)	94	91 (97)	< 0·001

Values in parentheses are percentages. SIRS, systemic inflammatory response syndrome. *χ^2 test.

It was not possible to determine whether SIRS preceded early organ dysfunction. Thirty (57 per cent) of the 53 patients who had early organ dysfunction presented with it on admission. This finding was not explained by duration of symptoms. The median duration of symptoms was 24 h, both in patients who presented with established organ dysfunction and in those who developed organ dysfunction after admission to hospital. The 23 patients who developed organ dysfunction during admission did so at a median of 24 h after admission; six patients died in this group. Twelve patients had resolving organ dysfunction and 11 had deteriorating organ dysfunction (including the six who died)

Discussion

The main finding of this study was that organ dysfunction that resolved during the first week had a benign course and did not contribute to mortality. The current definition of severe acute pancreatitis which includes all patients with organ dysfunction[12] should be modified to include only those with deteriorating organ dysfunction, as defined by a worsening organ dysfunction score during the first week of the disease.

Patients in this study were recruited from a randomized clinical trial of the platelet-activating factor antagonist lexipafant. It is not likely that this affected the outcome as this large multicentre study of 1518 patients showed no benefit[25]. By including only patients who had had symptoms for less than 48 h and an APACHE II score of more than 6, a large group of patients with mild pancreatitis was excluded. Occasionally patients with initially mild pancreatitis may develop organ dysfunction at a later stage, but a very large study including all patients with acute pancreatitis would be necessary to define the incidence of these patients. Previous experience is that this would be very rare[26].

More than half (57 per cent) of the 53 patients who had any organ dysfunction in this study had established organ dysfunction on admission. This highlighted four important points. First, organ dysfunction is a dynamic process that begins very early, probably within hours of the onset of acute pancreatitis, which may then improve, persist or worsen. A window of opportunity to prevent organ dysfunction from developing in these patients is either non-existent or very small. If organ dysfunction is already apparent on admission in the majority of patients, this brings into question the value of predictive systems. The presence of organ dysfunction on admission was not explained by the duration of illness, suggesting different mechanisms of disease. At least two studies of patients with multiple trauma found a similar bimodal phenomenon in the onset of multiple organ dysfunction[27,28]. Further research would be necessary to clarify this observation in acute pancreatitis.

The presence of organ dysfunction on admission also reduced the number of patients who could be included to analyse the temporal relationship between SIRS and early organ dysfunction. Persistent SIRS correlated with survival and might be useful to predict deteriorating early organ dysfunction. If these observations can be confirmed in a larger, less selective, population of patients with acute pancreatitis, SIRS could become a bedside indicator of severity.

Respiratory failure is common during the first week in patients with acute pancreatitis[29] and in the present study accounted for the majority of patients with mild organ dysfunction that resolved. The majority of deaths, however, were due to respiratory failure followed by sequential failure of other organ systems.

Early organ dysfunction in acute pancreatitis is usually self-limiting, but in a small group of patients it deteriorates. It is in this group that death from acute pancreatitis occurs. Rapidly resolving early organ dysfunction should be excluded from definitions of severe acute pancreatitis. Future trials of anti-inflammatory agents should be aimed at the high-risk group of patients with deteriorating organ dysfunction. The dynamics of changing organ dysfunction scores are crucial with respect to outcome in acute pancreatitis.

Acknowledgements

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Original article

Phase I study of percutaneous cryotherapy for colorectal liver metastasis

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Background: The aim was to determine the safety and feasibility of percutaneous cryotherapy for treating irresectable colorectal liver metastases.

Methods: Liquid nitrogen cryoprobes were inserted percutaneously into metastases using the Seldinger technique under computed tomographic guidance. Single-probe treatments were performed with either 3·6- or 6·3-mm cryoprobes (ice-ball volumes 18 and 59 cm^3 respectively), or dual-probe treatments with two adjacent 6·3-mm probes (ice-ball volume 205 cm^3). Treatment involved a single freeze–thaw cycle.

Results: Fifteen patients received 25 single-probe treatments and seven patients received 14 dual-probe treatments. The treatment-related mortality rate was zero and complications occurred after six of 39 treatments. Liver metastasis growth was significantly delayed for 2 months after dual-probe but not single-probe treatment. Metastasis cryotherapy stimulated an immediate rise, followed by a fall, in serum carcinoembryonic antigen (CEA) level, associated with immune upregulation that was significantly greater after dual-probe treatments.

Conclusion: Ablation zones that were approximately four times larger than those produced by previously described percutaneous techniques delayed the growth of metastases, reduced serum CEA concentration, and induced detectable inflammatory and T-lymphocyte responses. Percutaneous cryotherapy for treatment of colorectal liver metastases is feasible and may have a place in conjunction with chemotherapy.

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Introduction

Liver metastases develop in 30–50 per cent of patients with colorectal cancer[1]. Without treatment, the median survival is approximately 7 months[2]; few affected patients survive more than 5 years. Resection of metastasis is suitable in 7–10 per cent of affected patients although fewer than one-third of these will survive 5 years[1]. Although chemotherapy produces some survival benefit[2,3], tumour resistance to chemotherapy limits longer survival benefit in most patients. A treatment that ablated persisting liver metastases during chemotherapy might improve the duration of response, either by reducing residual tumour volume or by inducing an inflammatory response within the tumour[4].

Interstitial ablation of colorectal liver metastases by yttrium–aluminium–garnet laser[5], high-frequency electric current[6], focused ultrasound[7] and freezing[8] has been described. In most cases these have been directed by visualizing metastases at laparotomy[8] or laparoscopy[9,10]. Image-guided percutaneous laser[11] and radiofrequency[12] ablation have also been developed. Use of percutaneous interstitial ablation as an adjunct to chemotherapy requires that the largest possible ablative volume is achieved, in order to ablate metastases of the size that are commonly encountered clinically, while retaining low morbidity to allow frequently repeated day-case administration. Although radiofrequency ablation can be performed percutaneously, the size of the lesions destroyed is generally less than 5 cm in diameter[13, 14]. Of the techniques available, cryotherapy is currently capable of producing the largest ablated volume (up to 10 cm in diameter). Apart from case

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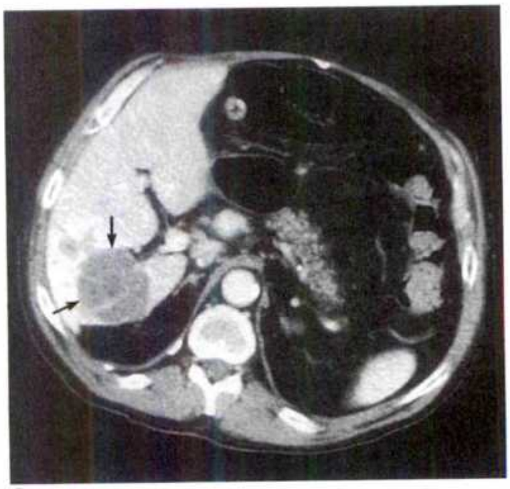
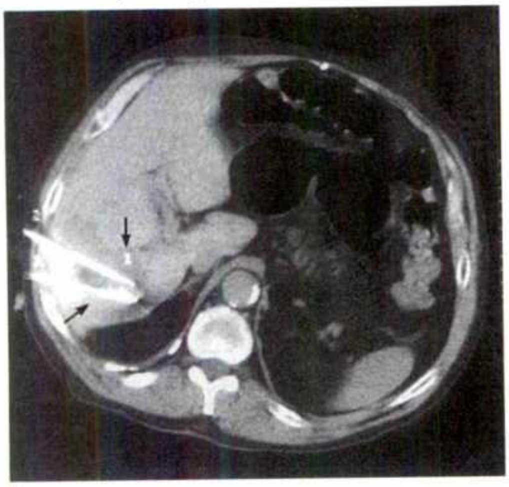
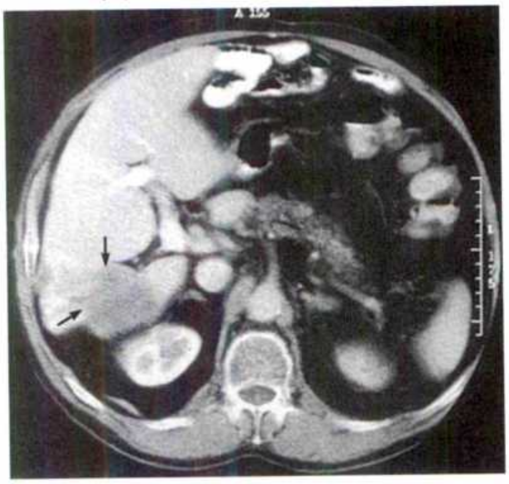


a Before cryotherapy



b After cryoprobe insertion



c 8 weeks after cryotherapy

Fig. 1 Computed tomograms showing one of the multiple liver metastases (black arrows) from a patient with bilobar liver metastases **a** before cryotherapy, **b** after cryoprobe insertion and **c** 8 weeks after cryotherapy

reports[15–17], there has been no systematic attempt to evaluate its potential for percutaneous image-directed ablation of metastases.

In the present study, the safety and feasibility of percutaneous image-directed cryotherapy was determined in the treatment of colorectal liver metastases. In addition, the effect of different ice-ball volumes on changes in tumour-related and inflammatory indices was assessed.

Patients and methods

Between July 1996 and December 1999, patients aged 75 years or less were studied who had either irresectable colorectal liver metastases or co-morbidity that precluded resection. Metastases were deemed irresectable if they were bilobar and multifocal, or if they invaded major vascular structures. Patients with metastases greater than 5 cm (single-probe study) or 7 cm (dual-probe study) in diameter were excluded. Patients with more than five metastases, or extrahepatic disease identified by abdominal computed tomography (CT) or chest radiography, were also excluded. Early in the study, all patients underwent single-probe cryotherapy; subsequently patients received dual-probe treatments. All patients gave written informed consent, and the study was approved by the Chelsea and Westminster Hospital Research Ethics Committee.

Cryotherapy technique

Ultrasonographic guidance (Hitachi EUB 415; Hitachi Medical Corporation, Tokyo, Japan) was used for the first five single-probe treatments, but needle placement was accurate in only two patients. Subsequently all guidewire insertions were directed by CT (Siemens Somatom Plus 4; Siemens, Forchheim, Germany), and the procedure was undertaken within the CT suite.

Under general anaesthesia, abdominal CT was performed (*Fig. 1*) and a 19-Fr needle was inserted percutaneously into a selected liver metastasis. After checking the needle position by CT, a guidewire was placed through the lumen of the needle into the metastasis and the needle withdrawn. A track for the insertion of a peel-away sheath was made by passing dilators (William Cook, Bjaeverskov, Denmark) over the guidewire, up to a maximum of 20 Fr (for insertion of the 6·3-mm diameter probe). A cryoprobe (Spembly Medical, Andover, UK) was then passed through the peel-away sheath into the tumour. The sheath was split and partially withdrawn to allow the uninsulated tip of the insulated cryoprobe to come into contact with the tumour (*Fig. 1*).

Single-probe treatments were performed with either 3·6- or 6·3-mm diameter cryoprobes. These produced ice-ball

Table 1 Details of the 17 patients who received 39 cryotherapy treatments for colorectal liver metastases

Gender (M : F)	10 : 7
Age (years)	64 (58–66)
No. of liver metastases per patient	3 (1–6)
Cryotherapy treatments per patient	2 (1–3)
Interval between cryotherapy treatments (weeks)	14 (11–24)
No. of metastases treated per patient	1 (1–2)
Hospital stay per patient per treatment (days)	3 (3–4)
Survival from first cryotherapy treatment (days)	395 (168–548)

Values are median (interquartile range)

volumes of 18 and 59 cm^3 respectively in *in vitro* studies carried out at body temperature. Dual-probe treatments were done with two 6·3-mm probes placed in parallel with the tips situated 2 cm apart to produce a single 205-cm^3 ice-ball. Each treatment involved one freeze cycle lasting 20 min to avoid the coagulopathy and multiorgan failure associated with multiple freeze–thaw cycles[18]. Temperatures at the tip of the 3·6- and 6·3-mm probes during freezing reached – 196°C and – 180°C respectively within 5 min of commencing freezing. After the 20-min freeze, passage of warmed nitrogen through the probe assisted thawing, and the probe was removed once the frozen attachment of the cryoprobe tip to the tumour was detached by warming to above 0°C (approximately 12 min of thawing). After probe removal, the probe track was embolized with Gelfoam slurry (Johnson & Johnson Medical, Skipton, UK) during withdrawal of the peel-away sheath. Patients returned to a recovery monitoring area for 4 h after treatment and were then observed in hospital for a further 36 h, where protocol blood sampling was done.

Variables measured

Treatment-related complications occurring within the month after treatment were recorded. Peripheral venous blood was taken before, and at 1, 14, 28, and between 40 and 60 days after cryotherapy treatment. Full blood count, C-reactive protein (CRP), interleukin 6 (IL-6), interleukin 2 soluble receptor α (IL-2 sRα), soluble tumour necrosis factor receptor I (sTNF RI), carcinoembryonic antigen (CEA) and plasma liver enzymes were measured. CRP concentrations of up to 10 mg/l were taken as within the normal range. Normal median (range) serum values were 1·6 (0·4–10·1) ng/l for IL-6, 1346 (676–2132) ng/l for IL-2 sRα and 1198 (749–1966) ng/l for sTNF RI. The volume of metastasis was measured before and 2 months after cryotherapy by CT with intravenous contrast, as described previously[19].

Statistical analysis

Changes in variables before and after cryotherapy were assessed by the Wilcoxon signed rank test. Comparison of variables between single- and dual-probe groups was by the Mann–Whitney *U* test. Correlation between different variables was performed with the Spearman test.

Results

Patients, treatments and survival

Thirty-nine cryotherapies were performed in 17 patients (*Table 1*). All patients had received, and five patients were concurrently receiving, systemic fluorouracil and folinic acid chemotherapy. Fifteen patients received 25 single-probe treatments, seven received 14 dual-probe treatments, and five patients received ten single- and nine dual-probe treatments. There were no deaths within 30 days of cryotherapy treatment, and no subsequent deaths were attributed to cryotherapy-related complications.

Complications

Complications occurred after six of the 39 treatments as follows. (1) Liver haemorrhage after dual-probe cryotherapy. At laparotomy performed 5 h after cryotherapy, a bleeding artery on the hepatic capsule at the site of probe puncture was oversewn. The patient was discharged from hospital 7 days after laparotomy. (2) Obstructive jaundice immediately following single-probe cryotherapy treatment. A stricture adjacent to the cryotherapy site near the liver hilum was later identified and stented at percutaneous transhepatic cholangiography. (3) Right-sided pleural effusion requiring percutaneous drainage, after dual-probe cryotherapy of a metastasis situated close to the diaphragm. (4) Nodal bradycardia (40 beats per min) resistant to intravenous atropine during single-probe freezing of a liver segment II lesion situated close to the base of the heart. Freezing was discontinued and normal cardiac rhythm returned spontaneously when the probe temperature reached 20°C. (5) A 4-cm^2 area of skin necrosis requiring debridement, between dual probe skin entry sites for cryotherapy of a superficially located liver metastasis. The cutaneous cavity was healed within 2 months after cryotherapy treatment. (6) Right-sided axillary and musculocutaneous neuropraxia after single-probe cryotherapy. While anaesthetized, the patient was supine in the CT scanner with the right forearm carefully positioned above the head to allow cryoprobe access below the right costal margin. Following treatment there was weakness of right shoulder abduction and elbow flexion, numbness in the upper arm, and absent ipsilateral bicipital and supinator reflexes. Axillary and musculocutaneous neuropraxia was confirmed by nerve conduction and electromyography studies; symptoms resolved within 3 months.

Metastasis volume and serum carcinoembryonic antigen level

A change in metastasis image signal was not usually detectable between CT scans taken before and at 8 weeks after treatment (*Fig. 1*). There was a significant increase in the volume of the treated metastasis between baseline and 2 months after single-probe (median (interquartile range (i.q.r.) 23 (13–53) *versus* 57 (14–137) ml respectively; P = 0·05) but not after dual-probe (144 (124–279) *versus* 178 (120–277) ml respectively) treatment (*Fig. 2*).

Sixteen of the 17 patients had CEA-producing tumours as indicated by increasing serum levels before cryotherapy treatment. The serum CEA level rose significantly above baseline on the first day after cryotherapy and then fell to significantly below the pretreatment level at between 14 and 28 days after dual-probe cryotherapy. Similar significant changes did not occur after single-probe treatment. The increase in serum CEA level above baseline at day 1, as well as subsequent decreases at 14 and 28 days, were significantly greater after dual-probe cryotherapy (day 1, P < 0·01; day 14, P = 0·04; day 28, P < 0·01; *Fig. 3*). Serum CEA levels between 40 and 60 days after cryotherapy were significantly increased over baseline after single- but not after dual-probe cryotherapy (*Fig. 3*). There were significant correlations between the extent of the CEA rise on day 1 and the fall on days 14 (r_S = − 0·59 (95 per cent confidence interval (c.i.) − 0·82 to − 0·20); P < 0·01), day 28 (r_S = − 0·59 (− 0·80 to − 0·26); P < 0·01) and days 40–60 (r_S = − 0·54 (− 0·82 to − 0·07); P = 0·03).

Inflammatory markers

There were significant increases in leucocyte counts above baseline on the first day after dual- and single-probe cryotherapies (*Fig. 4*) that were significantly greater (P = 0·02) at 14 days after treatment with dual compared with single cryoprobes. Similarly, there were significant rises in serum CRP level above baseline with both single- and dual-probe treatments that were significantly greater on day 1 after treatment (P = 0·01) and more sustained at 14 days (P < 0·01) for dual-probe treatments. Serum IL-6 and sTNF RI levels also increased significantly above baseline on the first day after treatment, before returning to normal by 14 days after both single- and dual-probe cryotherapy (*Fig. 4*). The serum IL-2 sRα level was significantly above baseline at 1 and 14 days after dual-probe cryotherapy; the increase in IL-2 sRα was significantly greater (P = 0·04) at 14 days after dual-probe cryotherapy.

Relation between tumour and inflammatory response

Compared with baseline values, the increase in serum CEA concentration on the first day after cryotherapy for both dual and single probes correlated significantly with the

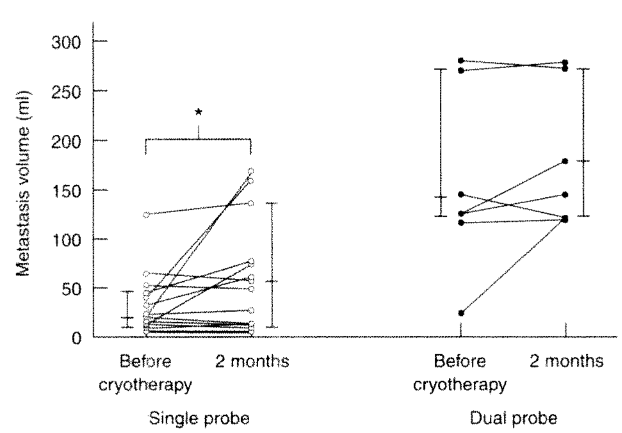


Fig. 2 Changes in liver metastasis volume measured by computed tomography 8 weeks after cryotherapy. Bars represent median and interquartile ranges. There was a significant increase in metastasis volume after single- but not dual-probe treatments. *P ≤ 0·05 (Wilcoxon signed rank test)

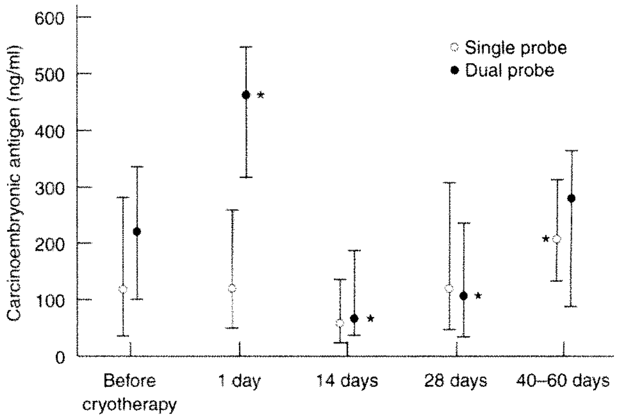
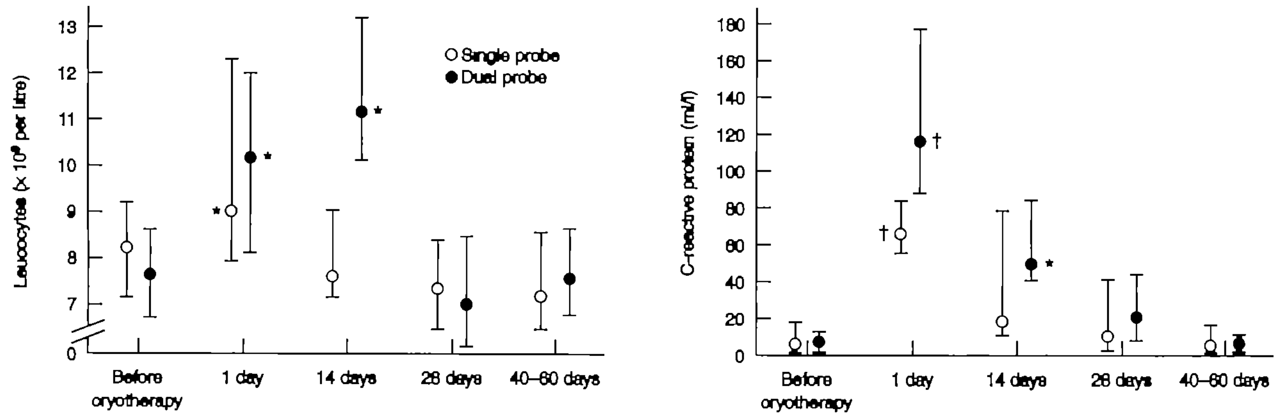


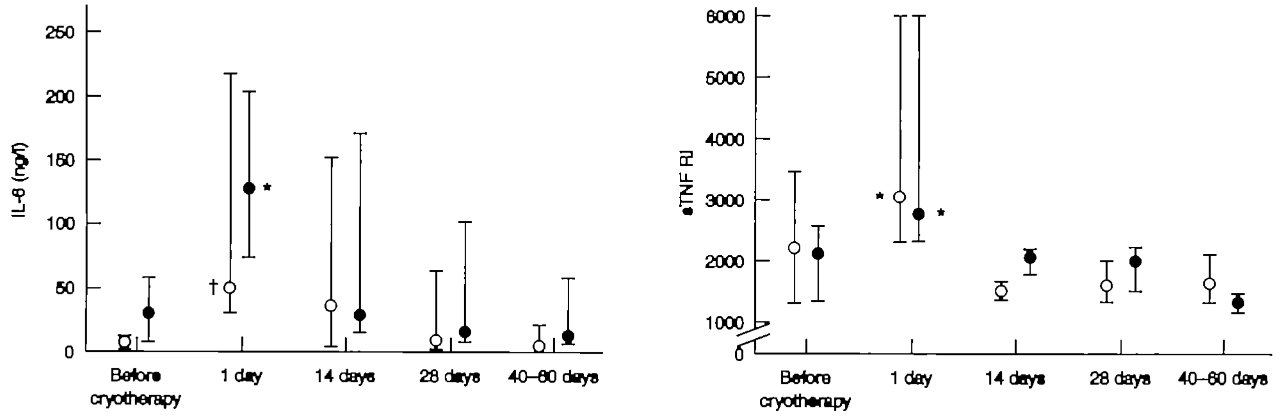
Fig. 3 Changes in serum carcinoembryonic antigen level after single- or dual-probe cryotherapy. Values are median and interquartile range. There was an immediate significant rise followed by a significant fall below baseline which persisted for 28 days after dual- but not single-probe treatments. *P ≤ 0·01 *versus* baseline (Wilcoxon signed rank test)

increase in serum CRP ($r_S = 0{\cdot}39$ (95 per cent c.i. 0·01 to 0·68); $P = 0{\cdot}05$) and serum IL-2 sRα ($r_S = 0{\cdot}47$ (0·00 to 0·77); $P = 0{\cdot}05$). The fall in serum CEA levels 2 weeks after cryotherapy correlated significantly with the increase in serum CRP concentration ($r_S = -0{\cdot}54$ (–0·80 to –0·13); $P = 0{\cdot}01$). The change in serum CEA level did not correlate



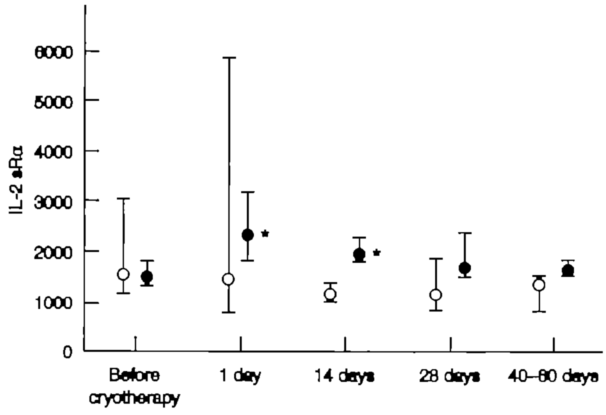
a Leucocytes

b C-reactive protein



c IL-6

d sTNF RI



e IL-2 sRα

Fig. 4 Changes in inflammatory markers after single- or dual-probe cryotherapy. Values are median and interquartile range. IL-6, interleukin 6; sTNF RI, soluble tumour necrosis factor receptor I; IL-2 sRα, interleukin 2 soluble receptor α. Significant inflammatory and T-lymphocyte responses were detected that were more marked after dual- than single-probe treatments. $^*P \leqslant 0{\cdot}05$, $^\dagger P \leqslant 0{\cdot}01$ *versus* baseline (Wilcoxon signed rank test)

significantly with changes in other immune products after cryotherapy.

Haemoglobin, platelet count and liver function tests

There was a significant fall in haemoglobin level after cryotherapy with both single- and dual-probe treatments that persisted for 14 days from dual-probe treatment (median (i.q.r) decrease 1·0 (0·6–1·8) g/dl; $P = 0{\cdot}01$) and for 28 days from single-probe treatment (median decrease 0·4 (0·1–1·0) g/dl; $P < 0{\cdot}01$). The platelet count fell significantly on the first day (median (i.q.r.) decrease 41 (18–57) $\times 10^9$ per litre with single probe, $P < 0{\cdot}01$; 58 (46–96) $\times 10^9$ per litre with dual probe, $P < 0{\cdot}01$), followed by a significant rise above baseline at 14 days (median (i.q.r.) increase 80 (47–118) $\times 10^9$ per litre with single probe, $P < 0{\cdot}01$; 165 (116–195) $\times 10^9$ per litre with dual probe, $P < 0{\cdot}01$), before returning to baseline level at 28 days (single probe) or 40–60 days (dual probe) after treatment. Platelet count increases were significantly greater after dual- than single-probe treatments at 14 and 28 days after cryotherapy ($P = 0{\cdot}01$ and $P = 0{\cdot}05$ respectively).

Significant increases above baseline in plasma bilirubin (median (i.q.r.) increase 7 (2–14) µmol/l with single probe, $P < 0{\cdot}01$; 8 (6–11) µmol/l with dual probe, $P < 0{\cdot}01$) and alanine transaminase (median (i.q.r.) increase 158 (43–261) units/l for single probe, $P < 0{\cdot}01$; 222 (180–299) units/l for dual probe, $P < 0{\cdot}01$) levels were found on the first day but had returned to normal by 14 days after both single- and dual-probe treatments. Significant changes in plasma alkaline phosphatase concentration were not detected.

Discussion

A treatment-related mortality rate of 2 per cent has been reported after laparotomy-directed cryotherapy of liver metastases[18]. It is encouraging that there were no treatment-related deaths with the percutaneous approach, but a much larger experience is required. The complication rate (15 per cent) was similar to that (18 per cent) reported after laparotomy-directed cryotherapy[18]. In the present study two probes of 6·3 mm diameter were inserted in parallel to achieve an ablation zone of 205 cm^3, approximately four times larger than that reported with percutaneous radiofrequency[13,14] or laser[11] ablation.

The development of smaller-calibre cryprobes capable of producing large ice-balls might reduce the risks of cryoprobe insertion into the liver, and allow larger ice-balls to be created with multiple cryoprobes. Liquid argon technology allows smaller-calibre cryoprobes[20], but the ice-ball volume is less than that with liquid nitrogen[21]. Injury to major hepatic ducts can be reduced by avoiding cryoablation of lesions situated very close to the liver hilum. Although treatment of lesions located close to the diaphragm resulted in pleural effusion and cardiac arrhythmia, other similarly situated lesions were treated without complication. Pleural effusion has been reported after open cryotherapy[22] when up to 15 per cent of patients may require pleural drainage for symptomatic relief[23]. Cardiac monitoring is essential for patients undergoing percutaneous cryotherapy, and freezing should be discontinued if an arrhythmia develops.

Insulation of all but the 2-cm long probe tip should prevent cutaneous cryoinjury unless there is retrograde extension of the most superficial portion of the ice-ball into the abdominal wall. This risk can be reduced by starting the freeze cycle only when the probe tip has been inserted deep into the metastasis. Where skin necrosis is at higher risk because of a superficially located metastasis, adjacent skin temperature can be monitored. Despite careful positioning, one patient sustained a nerve injury in the right arm. A specific cause could not be identified in this case, and no difficulties arose with more than 20 subsequent treatments using standard precautions. The constrained patient position within the CT scanner, the duration of the procedure, and the calibre and depth of probe insertion favoured general anaesthesia for this developmental study. Local anaesthesia for percutaneous cryotherapy may be feasible, but the potential for cardiac or haemodynamic instability requires continuous monitoring of vital signs.

Serum CEA concentration has been reported to fall after open colorectal liver metastasis cryotherapy[24], and the extent of reduction correlates with survival[8]. The present study identified an early and steep rise in serum CEA level after percutaneous cryotherapy, which may have resulted from tumour cryoinjury. This was supported by the finding of a correlation between the initial CEA rise and subsequent CEA fall at 14, 28 and 40–60 days after treatment. This rise may previously have been obscured by changes related to laparotomy or liver mobilization in open cryotherapy studies. A significant fall in serum CEA level below baseline was detected after dual-probe, but not single-probe, cryotherapy. By 40–60 days after treatment, the serum CEA level had not increased significantly from baseline with the dual probe but had risen significantly above baseline after single-probe treatment. Thus an approach based on preventing a rise in serum CEA concentration, by percutaneous dual-probe treatment repeated approximately every 8 weeks is feasible and might offer disease control. Percutaneous cryotherapy allows regular repeated treatment for either an incompletely ablated or another metastasis.

Cryotherapy-induced changes are difficult to distinguish from residual disease on CT (*Fig. 1*)[25]. Since cryotherapy aims to destroy the lesion with a clearance margin around it, the subsequent tumour size may be overestimated if this margin resembles the treated tissue. This may be one reason for the lack of reduction in metastasis volume after dual-probe cryotherapy despite a fall in serum CEA level. The reduction in serum CEA concentration and the stabilization of metastasis volume over 2 months with dual-probe, but not single-probe, cryotherapy suggests that the former was more effective.

Both the extent of the CEA rise on day 1 and the fall by day 14 after cryotherapy correlated with the increase in serum CRP levels, suggesting that the extent of inflammatory response to cryotherapy correlated with tumour injury. The increase in IL-6 concentration on the day after cryotherapy reflected an acute-phase protein response to cryoinjury[26] that was associated with increased hepatic CRP release which persisted for 14 days. The finding of greater increases in leucocyte count and serum CRP levels with dual-probe treatment suggested a greater inflammatory effect with the larger volume ablated by dual probes. The rises in sTNF RI and IL-2 sRα concentration suggested a T-lymphocyte response[27] to antigens released by cryoinjury, which was more durable after dual-probe treatment.

There was a 23 per cent fall in circulating platelet count on the day after treatment that was followed by a 41 per cent rise above baseline by day 14, which was greater with dual-probe treatments. Similar changes after open cryotherapy[28] have been attributed to reticuloendothelial platelet sequestration[29] since they do not occur in the absence of the spleen[28]. Cryotherapy-associated coagulopathy was not detected.

Intraoperative ultrasonographic guidance is the preferred method for directing the cryoprobe in open cryotherapy[30–32]. However, the advantages of intraoperative ultrasonography were not translated to transabdominal ultrasonography used for percutaneous treatment. Placement of cryoprobe with ice-ball formation was accurate in only two of the initial five ultrasound-directed treatments. During open cryosurgery the ultrasound probe can be moved over the liver surface, thereby maintaining an adequate sonic view[33]. Transabdominal ultrasonography could not visualize the posterior aspect of the ice-balls because ice prevents sound wave penetration[34]. The feasibility of percutaneous cryotherapy with CT guidance has been reported previously in an animal model[35], but its limitation is lack of real-time control. Combining CT with a programmed robotic probe inserter may overcome this problem[36]. A further drawback of CT is the inability to record the temperature gradient within the ice-ball. Interventional magnetic resonance (MR) imaging overcomes this, and the development of both open-configuration MR imaging systems and the availability of MR-compatible cryoprobes has enabled the delivery of percutaneous cryotherapy into liver tumours[37].

The optimal role of percutaneous cryotherapy for colorectal liver metastases may be in combination with chemotherapy[38]. The aim would be for cryotherapy to reduce tumour load, while chemotherapy controlled residual disease and microscopic metastases. Current studies of cryotherapy with chemotherapy have not shown a survival benefit compared with cryotherapy alone[39]. However, based on previous experience of changes in serum CEA after systemic fluorouracil with folinic acid chemotherapy for colorectal liver metastases[40], and the serum CEA changes achieved with dual-probe cryotherapy in the present study, a randomized comparison of the effectiveness of repeated percutaneous cryotherapy and systemic chemotherapy compared with systemic chemotherapy alone is justified. A study to compare the reduction in serum CEA levels would require 460 patients in each arm with an 80 per cent power of detecting significant differences at the 95 per cent confidence level. A large multi-institutional study will be needed.

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Original article

Estimation of prognosis after hepatectomy for hepatocellular carcinoma

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Background: The preferred means of treatment for hepatocellular carcinoma is surgical resection. However, the tumour recurrence rate is high. Accurate estimation of the risk of tumour recurrence after hepatectomy may facilitate the administration of adjuvant therapy after hepatectomy to patients with a high likelihood of tumour recurrence.

Methods: The clinical and pathological profiles of 176 patients undergoing hepatectomy for hepatocellular carcinoma from March 1992 to August 1998 were reviewed. The Kaplan–Meier method and log rank test were used to analyse univariate prognostic factors. The Cox proportional hazard model was used for multivariate analysis. Disease-free and overall cumulative survival rates were estimated with respect to the number of prognostic factors.

Results: Independent factors associated with a lower disease-free survival included the presence of venous infiltration, presence of daughter tumours, absence of tumour encapsulation and tumour size exceeding 5 cm. Factors decreasing the overall survival rate included the presence of venous infiltration, absence of tumour encapsulation and surgical resection margin less than 1 cm. The 1-year disease-free survival rate decreased from 77·5(s.e. 5·6) to 14·0(8·5) per cent when the number of risk factors present increased from zero to three. The 5-year survival rate decreased from 60·2(11·7) per cent to zero when the number of risk factors increased from zero to three.

Conclusion: The deterioration of disease-free or overall survival of patients with hepatocellular carcinoma after hepatectomy correlates with increasing number of risk factors. The number of risk factors can be employed to accurately estimate disease-free and overall survival.

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Introduction

Hepatocellular carcinoma (HCC) is a common malignancy worldwide. Surgical resection is the preferred treatment and provides the best results of all the available therapeutic modalities[1,2]. However, the prognosis of HCC after surgical resection remains poor. The 5-year survival of patients undergoing surgical resection for HCC is only 30–40 per cent[3–6]. A high tumour recurrence rate after hepatectomy is the most important factor leading to unsatisfactory results after surgical treatment[7–9]. Chen *et al.*[10] reported a tumour recurrence rate as high as 59 per cent in the first year after hepatectomy. To improve patient survival after hepatectomy for HCC, posthepatectomy adjuvant therapy to prevent tumour recurrence or reduce the recurrence rate is essential.

Possible adjuvant therapies after hepatectomy include transcatheter arterial chemoembolization, chemotherapy[11,12] and immunotherapy[13,14]. However, all these treatments may have adverse effects, and patient selection in desirable. The identification of patients at high risk of tumour recurrence after hepatectomy is essential in order to select those in whom adjuvant therapy is necessary. Several factors have been suggested to predispose to tumour recurrence[9,15–17] but it has not been possible to predict those who are at risk.

This retrospective study reviewed the profiles of patients who had undergone surgical resection for HCC to identify the risk factors for tumour recurrence and determined whether the number risk factors present can be employed to forecast the recurrence rate after hepatectomy.

Patients and methods

The clinical and pathological profiles of patients who underwent hepatectomy for HCC from March 1992 to

August 1998 were reviewed. One hundred and seventy-six patients (136 men and 40 women) with complete clinical and pathological data were enrolled in this study for overall survival analysis. Only 168 patients were included in the analysis of disease-free survival because the exact dates of tumour recurrence were missing in eight patients. The general profiles and clinicopathological data are shown in *Table 1*. Most of the patients (64·2 per cent) were infected with hepatitis B (defined as being positive for hepatitis B surface antigen) and 31·8 per cent had hepatitis C (positive for antihepatitis C antibody). For analysing the influence of tumour factors on tumour recurrence and patient survival, tumour size, venous infiltration, tumour encapsulation, presence of daughter tumours and surgical resection margin were all recorded.

Follow-up

Patients were regularly followed up clinically. Liver function tests, α-fetoprotein measurements and liver sonography were performed every 2–3 months. Computed tomography (CT) was performed if deemed necessary. Tumour recurrence was recorded when sonography or CT detected a tumour. The median follow-up interval was 23·5 (range 2–76) months. Disease-free survival was measured from the date of hepatectomy until tumour recurrence. Overall survival was measured from the date of hepatectomy until death.

Table 1 Clinical features of 176 patients enrolled in the study

Mean(s.d.) age (years)	53·8(13·5)
Sex	
Male	136 (77·3)
Female	40 (22·7)
Cirrhosis	
No	76 (43·2)
Yes	100 (56·8)
Child grade	
A	79 (44·9)
B	20 (11·4)
C	1 (0·6)
Operative procedure	
Right lobectomy	43 (24·4)
Left lobectomy	32 (18·2)
Extended right or left lobectomy	12 (6·8)
Segmentectomy	89 (50·6)
Hepatitis status	
B(−) C(−)	20 (11·4)
B(+) C(−)	100 (56·8)
B(−) C(+)	43 (24·4)
B(+) C(+)	13 (7·4)

Values in parentheses are percentages unless otherwise stated

Analysis of prognostic factors

Disease-free and overall survival were correlated with clinicopathological variables to determine prognostic factors. Factors analysed included sex, presence of liver cirrhosis, presence of hepatitis, serum level of α-fetoprotein, maximum tumour size, tumour encapsulation, venous infiltration, presence of daughter nodules and surgical resection margins. Survival rates were calculated by the Kaplan–Meier method and compared between groups by the log rank test. $P < 0{\cdot}05$ was considered statistically significant.

Multiplicity of prognostic factors to estimate survival

Multivariate analysis of the prognostic factors was performed by using the Cox proportional hazard model to identify independent prognostic factors. The disease-free and overall survival rates according to the number of significant prognostic factors were calculated by the Kaplan–Meier method. In addition, groups with various numbers of prognostic factors were compared by the log rank test. $P < 0{\cdot}05$ was considered statistically significant.

Results

Survival rates and prognostic factors

Using Kaplan–Meier analysis the disease-free and overall survival rates of all patients undergoing hepatectomy were calculated. The 1-, 3- and 5-year disease-free cumulative survival rates were 53·5(s.e. 3·4), 35·1(3·8) and 21·8(6·2) per cent respectively. The respective overall cumulative survival rates were 79·5(2·7), 52·3(4·1) and 34·2(5·7) per cent. Examination of prognostic factors by the log rank test revealed that tumour size larger than 5 cm in diameter, absence of tumour encapsulation, presence of venous infiltration, presence of daughter tumours and presence of hepatitis B diminished the disease-free survival (*Table 2*). Tumour size larger than 5 cm in diameter, absence of tumour encapsulation, presence of venous infiltration, presence of daughter nodules and a resection margin less than 1 cm decreased the overall survival rate (*Table 3*).

Cox multivariate analysis

Cox multivariate analysis further confirmed the significance of the prognostic variables. Four factors, i.e. presence of venous infiltration, presence of daughter tumours, absence of tumour encapsulation and tumour size larger than 5 cm, significantly decreased disease-free survival (*Table 4*). Three factors, i.e. presence of venous infiltration, absence

Table 2 Prognostic factors of disease-free survival by univariate analysis

	No. of patients	Mean survival time (months)	*P*
Sex			0·198
Male	128	24·6(2·3)	
Female	40	39·6(5·8)	
Cirrhosis			0·320
Yes	94	31·0(3·6)	
No	74	25·0(3·3)	
Child grade			0·137
A	76	27·3(3·1)	
B	18	52·4(8·9)	
α-Fetoprotein (ng/ml)			0·166
< 20	64	30·5(4·0)	
≥ 20	104	27·1(3·1)	
α-Fetoprotein (ng/ml)			0·066
< 400	109	29·7(3·0)	
≥ 400	59	24·3(3·8)	
Tumour size			< 0·001
< 5 cm	102	35·6(3·6)	
≥ 5 cm	66	17·1(2·4)	
Tumour encapsulation			< 0·001
Present	115	34·4(3·4)	
Absent	53	17·5(3·0)	
Venous infiltration			< 0·001
Present	36	13·2(2·6)	
Absent	132	32·3(3·0)	
Daughter tumour			< 0·001
Present	36	11·7(2·0)	
Absent	132	34·2(3·2)	
Resection margin (cm)			0·104
≤ 1	103	26·2(3·7)	
> 1	65	31·2(3·6)	
Hepatitis B			0·003
Present	107	21·9(2·6)	
Absent	61	39·7(4·7)	
Hepatitis C			0·195
Present	55	33·6(4·7)	
Absent	113	25·1(2·7)	

Values in parentheses are s.e.

Table 3 Prognostic factors of overall survival by univariate analysis

	No. of patients	Mean survival time (months)	*P*
Sex			0·305
Male	136	40·6(2·5)	
Female	40	52·4(5·6)	
Cirrhosis			0·065
Yes	100	48·6(3·6)	
No	76	38·3(3·4)	
Child grade			0·344
A	79	44·2(3·1)	
B	20	59·3(8·6)	
α-Fetoprotein (ng/ml)			0·697
< 20	67	43·6(3·8)	
≥ 20	109	45·3(3·3)	
α-Fetoprotein (ng/ml)			0·113
< 400	114	44·6(3·0)	
≥ 400	62	41·2(4·1)	
Tumour size (cm)			0·003
< 5	106	50·2(3·5)	
≥ 5	70	35·6(3·5)	
Tumour encapsulation			0·007
Present	120	50·2(3·4)	
Absent	56	34·4(3·6)	
Venous infiltration			< 0·001
Present	40	23·4(3·0)	
Absent	136	51·3(3·1)	
Daughter tumour			0·008
Present	38	32·0(4·2)	
Absent	138	49·4(3·2)	
Resection margin (cm)			0·025
≤ 1	109	41·4(3·6)	
≥ 1	67	47·6(3·3)	
Hepatitis B			0·088
Present	113	38·9(2·8)	
Absent	63	51·1(4·5)	
Hepatitis C			0·226
Present	56	49·7(4·8)	
Absent	120	40·3(2·7)	

Values in parentheses are s.e.

of tumour encapsulation and resection margin less than 1 cm, significantly worsened overall survival (*Table 5*).

Disease-free survival calculated according to number of prognostic risk factors

Table 4 Prognostic factors of disease-free survival by multivariate analysis

	Hazard ratio	*P*
Presence of venous infiltration	2·06 (1·29, 3·30)	0·003
Presence of daughter tumours	2·04 (1·31, 3·19)	0·002
Absence of tumour encapsulation	1·72 (1·13, 2·62)	0·011
Tumour size ≥ 5 cm	1·62 (1·08, 2·43)	0·019
Presence of hepatitis B	0·69 (0·44, 1·08)	0·103

Values in parentheses are 95 per cent confidence intervals

Disease-free survival was calculated by the Kaplan–Meier method according to the number of prognostic risk factors. The risk factors (identified by Cox analysis) included presence of venous infiltration, presence of daughter tumours, absence of tumour encapsulation and tumour size larger than 5 cm. Disease-free survival was significantly worse in patients with a higher number of prognostic risk factors (*Fig. 1*). The 1-, 2-, 3- and 5-year disease-free survival rates in patients with different numbers of risk factors are listed in *Table 6*. Further analysis revealed that patients with one prognostic risk factor had a worse survival

Table 5 Prognostic factors of overall survival by multivariate analysis

	Hazard ratio	*P*
Presence of venous infiltration	3·30 (1·94, 5·62)	< 0·001
Absence of tumour encapsulation	2·11 (1·26, 3·54)	0·004
Resection margin ≤ 1 cm	1·82 (1·07, 3·11)	0·027
Presence of daughter tumours	1·49 (0·87, 2·57)	0·147
Tumour size ≥ 5 cm	1·52 (0·92, 2·50)	0·101

Values in parentheses are 95 per cent confidence intervals

Table 6 Cumulative disease-free survival rates according to number of prognostic risk factors

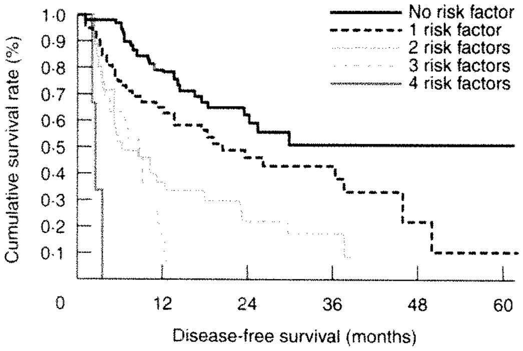
		Survival rate (%)			
No. of factors	No. of patients	1 year	2 years	3 years	5 years
0	59	77·5(5·6)	59·4(7·1)	51·9(8·0)	38·9(12·0)
1	52	62·9(6·8)	46·3(7·4)	43·2(7·5)	11·2(9·6)
2	35	36·6(8·2)	22·4(7·5)	17·9(7·2)	–
3	19	14·0(8·5)	–	–	–
4	3	0·0(0·0)	–	–	–

Values in parentheses are s.e.

Table 7 Cumulative overall survival rates according to number of prognostic risk factors

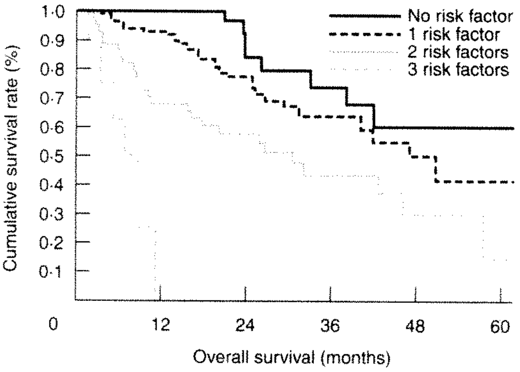
		Survival rate (%)			
No. of factors	No. of patients	1 year	2 years	3 years	5 years
0	39	100·0(0·0)	84·1(7·4)	73·8(9·4)	60·2(11·7)
1	85	92·9(2·8)	77·2(5·1)	64·0(6·6)	41·6(10·6)
2	44	67·9(7·1)	57·9(7·6)	43·4(8·6)	14·9(11·6)
3	8	0·0(0·0)	–	–	–

Values in parentheses are s.e.



No. at risk						
No risk factors	59	42	20	13	6	3
1 risk factor	52	29	17	14	2	1
2 risk factors	35	12	6	4	1	–
3 risk factors	19	2	–	–	–	–
4 risk factors	3	0	–	–	–	–

Fig. 1 Disease-free survival rates based on number of risk factors present. The prognosis diminishes as the number of risk factors increases. ($P < 0{\cdot}001$, Kaplan–Meier analysis)



No at risk						
No risk factors	39	36	20	14	8	6
1 risk factor	85	76	44	20	10	5
2 risk factors	44	29	22	10	4	1
3 risk factors	8	0	–	–	–	–

Fig. 2 Overall survival rates based on number of risk factors present. The prognosis diminishes as the number of risk factors increases. ($P < 0{\cdot}001$, Kaplan–Meier analysis)

rate than patients with no risk factors ($P = 0{\cdot}038$). Patients with two risk factors had a worse survival rate than patients with only one risk factor ($P = 0{\cdot}010$). However, the disease-free survival of patients with three risk factors did not differ from that of patients with two risk factors ($P = 0{\cdot}229$). All patients with four risk factors had tumour recurrence within 1 year and a significantly worse disease-free survival rate than patients with three risk factors ($P = 0{\cdot}008$).

Overall survival calculated according to number of prognostic risk factors

Overall survival was calculated by the Kaplan–Meier method with respect to the number of significant prognostic factors. The risk factors included presence of venous infiltration, absence of tumour encapsulation and resection margin less than 1 cm. The overall survival rate significantly worsened as the number of risk factors present increased (*Fig. 2*). The 1-, 2-, 3- and 5-year survival rates in patients with different numbers of risk factors are listed in *Table 7*. Patients with no risk factors and those with one factor did not have significantly different overall survival ($P = 0{\cdot}114$). However, the survival rate in patients with two risk factors was worse than that of patients with no risk factors ($P < 0{\cdot}001$) or one risk factor ($P = 0{\cdot}011$). Patients with all three risk factors had a worse survival rate than those with no risk factors ($P < 0{\cdot}001$), one risk factor ($P < 0{\cdot}001$) and two risk factors ($P < 0{\cdot}001$).

Discussion

The results of this study indicate that the number of prognostic factors can be used to accurately estimate the disease-free and overall survival rates after hepatectomy for HCC. Multivariate analysis of prognostic factors by the Cox proportional hazard model identified four and three significant factors that diminish the disease-free and overall survival rates respectively. By considering the number of independent prognostic factors present it may be possible to estimate disease-free and overall survival rates for a given patient; this has not been previously attempted for HCC after resection.

Determining the number of independent prognostic factors more accurately estimates the disease-free and overall survival rates after hepatectomy for HCC than the currently used pathological tumour node metastasis (TNM) system[18]. The TNM system is based on tumour size, venous infiltration, lobar distribution of tumours, lymph node status and distant metastasis. However, according to the multivariate analysis in this investigation, independent factors affecting disease-free survival include the presence or absence of venous infiltration, daughter tumours and tumour encapsulation, and tumour size. Independent factors affecting overall survival include the presence or absence of venous infiltration and tumour encapsulation, and surgical resection margin. The TNM system does not include important factors such as tumour encapsulation and daughter tumours in estimating disease-free survival, and tumour encapsulation and resection margin in overall survival. Izumi *et al.*[19] also contended that the TNM classification did not truly reflect prognostic significance and required modification. Marsh *et al.*[20] not only demonstrated that the currently used TNM system could not predict the outcome following liver transplantation for HCC but also proposed an alternative staging system. Determining the number of significant prognostic factors is more accurate than the TNM system in determining the prognosis for a resectable HCC after hepatectomy.

This analysis demonstrated that four independent factors, venous infiltration, daughter tumours, tumour encapsulation and tumour size, had an impact on the risk of tumour recurrence. Among these, venous infiltration by the tumour was the most significant factor to influence disease-free survival, followed by presence of daughter tumours. Although each factor differed in terms of influencing the disease-free survival rate, the data indicate that the tumour recurrence rate can be estimated simply by counting the number of significant factors; this information may be used to identify high-risk patients who need postoperative adjuvant therapy.

In this study, venous infiltration was the most important factor that reduced the overall survival, followed by tumour encapsulation. However, surgical resection margins also affected the overall survival rate.

HCC is a common malignancy with a poor prognosis, largely because of tumour recurrence after resection. This retrospective investigation identified four independent factors influencing disease-free survival and three factors influencing overall survival. In addition, simply determining the number of risk factors allowed estimation of the disease-free and overall survival. The 1-year disease-free survival rate declined from 77·5(5·6) to 14·0(8·5) per cent when the number of risk factors increased from zero to three. Similarly, the 5-year cumulative overall survival rate decreased from 60·2(11·7) when no risk factors were present to 14·9(11·6) per cent and zero for two and three factors respectively. In conclusion, the number of risk factors method can be employed to accurately and easily estimate disease-free and overall survival, and identify an individual patient who is at risk of tumour recurrence and in whom postoperative adjuvant therapy may be indicated.

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Original article

Right-lobe live donor liver transplantation improves survival of patients with acute liver failure

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Background: Right-lobe live donor liver transplantation (LDLT) is used by many liver transplant centres for treating adult patients with terminal liver disease, but its incremental benefit for the intended recipient over cadaveric liver graft transplantation has not been determined. The impact of LDLT as a proactive approach on the outcome of patients with acute liver failure was analysed.

Methods: From January 1999 to March 2001, right-lobe LDLT was offered proactively to 50 consecutive patients with acute liver failure and their families. The outcome of those who opted for right-lobe LDLT ($n = 34$) was compared with that of those who did not opt for LDLT ($n = 16$).

Results: In the group that opted for right-lobe LDLT, 16 patients eventually received a live donor right-lobe graft (14 patients survived) and three patients received a cadaveric liver graft that became available while the potential live donor was undergoing evaluation (all three patients survived). Among the group who did not opt for LDLT, only one patient received a cadaveric liver graft and survived. The former group had a higher overall survival rate (17 of 34 *versus* one of 16). With a proactive approach, the overall transplant rate was increased from four of 50 to 20 of 50. The morbidity rate among donors was low and none died.

Conclusion: Right-lobe LDLT improves the overall survival rate of patients with acute liver failure and should be considered as one of the treatment options for adult patients with acute liver failure.

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Introduction

Live donor liver transplantation (LDLT) using an extended right-lobe graft was initiated in 1996 for salvage of adult patients with acute liver failure[1]. Although the initial result was satisfactory, many surgeons have expressed concern about the risk to donors because about 65 per cent of the liver mass has to be removed from the donor. The operation was not therefore offered actively to the patient or his/her family at the time of interview. All the operations reported in a previous study were initiated by the patients' families[2]. However, in view of the severe shortage of cadaveric organ donors in Hong Kong (about one per million people per year), by January 1999 when confidence had been fully gained with the operation[3], the operation was offered as one of the options for patients with acute liver failure. In this study, the impact of LDLT using a right-lobe graft as a proactive approach on the outcome of patients with acute liver failure was analysed.

Patients and methods

From January 1999 to March 2001, 50 consecutive adult patients with acute or acute on chronic liver failure were studied prospectively. There were 13 patients with fulminant hepatic failure and 37 with acute exacerbation of chronic liver disease. Four patients had concomitant hepatocellular carcinoma. There were 38 men and 12 women with a median age of 45 (range 17–65) years. The decision to perform emergency liver transplantation for patients with fulminant hepatic failure was based on criteria established by King's College Hospital[4]. The decision to perform liver transplantation in patients with known hepatitis B and acute deterioration was based on the clinical judgement that a patient's life expectancy was less than 7 days without a liver transplant. All except five patients were managed in the intensive care unit. Patients with a suspected intracranial complication had computed tomography (CT) of the brain. Intracranial pressure monitoring was not done in any of the patients.

The need for emergency liver transplantation was explained to patients and their families at interview. They were informed of the source of a liver graft, either from a cadaveric or living donor, and the respective advantages and disadvantages. The overall result of local and overseas liver transplantation for acute liver failure, especially that related to live donor operation, was also explained at the interview. The right-lobe donor operation was described in detail. The operative risks of 1 per cent donor mortality and 30 per cent donor morbidity were also clarified. No coercion of live donation was made at any time. All donors were self selected and not doctor selected. The families were also told that their decision to accept LDLT would not preclude cadaveric liver transplantation if a cadaveric liver graft of matched blood group was available during assessment of the donor because patients with acute liver failure were given the highest priority for receiving a cadaveric liver graft.

Potential donors underwent preliminary investigation including detailed history, physical examination, assessment of blood group type, haematology, liver and renal biochemistry, and hepatitis B, hepatitis C and human immunodeficiency virus serology. Volunteers who were aged over 55 years or had medical disease were advised not to proceed with the donation. The volunteer was interviewed independently by the transplant surgeon, the physician taking care of the patient but not involved directly in the transplant operation and a clinical psychologist to ensure that the donor understood the nature of the operation, that the donation was truly voluntary and that reward in whatever form was not involved. The potential recipient, if conscious, was also interviewed by the clinical psychologist to ensure that he or she was willing to accept the liver graft from the potential donor and understood the nature of the operation. If the recipient was unconscious or incapable of understanding the explanation, an independent doctor certified in writing that the recipient was mentally incapacitated and it would not be in the best interest of the recipient to wait until he or she was able to understand an explanation given by the transplant surgeons. In the case of a lack of blood relationship between the donor and the recipient or if the latter was a spouse of less than 3 years, application to the local Human Organ Transplant Board for approval was made. When a donor withdrew consent for operation, the transplant team offered a medical reason of inappropriateness for donation.

Once the clinical psychologist had reported to the transplant team that the volunteer's intention to donate was truly voluntary and informed consent had been obtained, the potential donor was immediately evaluated by CT and hepatic arteriography. The volume of the left lobe and right lobe of the donor was assessed by CT[5]. The size of the donor's right lobe should be larger than 40 per cent of the recipient's standard liver volume[6]. The donor's left lobe should be greater than 30 per cent of the total liver volume and should have minimum steatosis[7]. When the suitability of liver donation was in doubt, liver biopsy or laparoscopy was performed. After completion of assessment of the donor, the potential recipient was re-evaluated to establish whether emergency liver transplantation was feasible. Potential recipients with uncontrolled sepsis, an escalating requirement for inotropes and intracranial complications were deemed unsuitable for liver transplantation.

The donor and recipient operations were performed as described previously[3]. In all cases, the middle hepatic vein was included in the right-lobe liver graft and the transection plane was exactly at the Cantlie's line. To prevent postoperative sepsis, the recipients received preoperative antibiotic cover that included amoxycillin and clavulanate (Augmentin® 1·2 g intravenously (GlaxoSmithKline, Worthing, UK)), rifampicin (300 mg intravenously over 1 h) and mupirocin cream (applied to the nasal cavity). The latter two drugs were for prevention of methicillin-resistant *Staphylococcus aureus* infection[8]. Bowel washout was done but decontamination was not given. Lamivudine was given orally for patients with hepatitis B viral infection once the decision to perform liver transplantation had been made, and was continued throughout and after the operation[9]. Hepatitis B immune globulin was not used. After operation the recipient received intravenous fluconazole 200 mg daily for prevention of fungal infection. Postoperative immunosuppression consisted of FK506 and steroid.

The study was approved by the Ethics Committee of the Faculty of Medicine, University of Hong Kong. Data of all donors and recipients were recorded prospectively in a liver transplant registry.

Results

Of the 50 patients in the study, the families of 16 did not opt for LDLT. Two of these patients had fulminant hepatic failure (acute hepatitis B, one patient; idiopathic cause, one) and 14 patients had acute exacerbation of chronic liver disease (chronic active hepatitis B, 12 patients; hepatitis C, one; chronic hepatitis B and C, one). Only one of them received a cadaveric liver graft after being placed on the transplantation list for 48 h and survived. All other 15 patients died between 24 h and 56 days (median 144 h) after listing. The causes of death were massive gastrointestinal bleeding (five patients), uncontrolled infection (four), uncontrolled heart failure (four), ruptured hepatocellular carcinoma (one) and multiorgan failure (one).

The 34 patients whose family members opted for live donor operation included 11 patients with fulminant hepatic failure (acute hepatitis B, four; acute hepatitis E, one; Wilson's disease, four; hepatic peliosis, one; idiopathic cause, one) and 23 patients with acute exacerbation of chronic hepatitis B infection. While waiting for completion of donor evaluation, cadaveric grafts became available to three patients, who survived after liver transplantation. The time from listing to liver transplantation for these three patients was 5, 7 and 20 days. Fifteen patients did not eventually undergo liver transplantation for the following reasons: four donors withdrew consent and four were not accepted as donors because of an unstable psychological condition (one), hepatitis B positivity (one), blood group incompatibility (one) and severe fatty change on CT (one); seven patients could not receive the liver graft in time partly owing to the delayed decision of the families to donate and partly because of a rapid deterioration in the patient's condition. These patients died from massive variceal bleeding (three), uncontrolled infection (two), small bowel gangrene (one), intracranial hypertension (one) and multiorgan failure (eight). The median time interval from listing to death in these 15 patients was 168 (range 24–576) h.

Sixteen patients received a right-lobe graft from a family member (wife, four; husband, one; brother, three; sister, three; son, one; aunt, one; brother-in-law, one) or friend (two). The median time from listing to liver transplantation was 48 (range 15–216) h for patients with fulminant hepatic failure and 72 (range 13–192) h for patients with acute on chronic liver failure. In 11 donors, the evaluation process was completed within 24 h of listing. Seven donors underwent laparoscopy before laparotomy. A normal liver was found in all except one who had mild fatty change on liver biopsy. Before liver transplantation, seven patients were supported by a mechanical ventilator. Hepatorenal syndrome was present in five patients, of whom three had received haemodialysis. Ten patients were in hepatic coma stage III/IV, and one had pulmonary infection. The median cold ischaemia time of the right-lobe grafts was 2·2 (range 1·3–3·7) h. The grafts weighed 430–950 (median 615) g and represented 39–89 (median 48) per cent of the estimated standard liver mass of the recipients.

All grafts functioned immediately after implantation. The international normalized ratio (INR) became normalized towards the end of the first postoperative week (*Table 1*). Massive ascites was not seen in any recipient. Two patients died after LDLT because of leakage from a bilioenteric anastomosis (one) and acute necrotizing pancreatitis (one). All other patients survived and were discharged from hospital between 14 and 43 (median 23) days after operation. No patient suffered from neurological deficit after liver transplantation. The 14 remaining patients are still alive at the time of writing (follow-up 6·2–33·1 (median 13·9) months). Pathological examination of explants from patients receiving a right-lobe live donor graft showed massive necrosis in six patients, chronic active hepatitis in seven patients, established cirrhosis in two patients and Wilson's disease in one patient.

Compared with the group of patients without volunteers, those who opted for LDLT had a higher chance of receiving a transplant (19 of 34 *versus* one of 16) and survival (17 of 34 *versus* one of 16). With a proactive approach to right-lobe LDLT, the transplant rate increased from four of 50 to 20 of 50. The overall survival rate of all patients managed in the study period was 36 per cent (18 of 50) (*Fig. 1*).

The age of the live donors ranged from 19 to 52 (median 40) years. No donor died or received blood transfusion. Massive ascites was not found in any donor. Donor morbidity included mild wound infection (three) and transient peroneal nerve palsy (one). The median liver remnant volume in the donors was 342 (range 220–488) ml, which represented 33 (range 24–41) per cent of the total liver volume estimated by CT volumetry. The donors were discharged from hospital between 6 and 30 (median 10) days after operation. There was no major abnormality in the haemoglobin concentration, platelet count, INR and serum bilirubin or aspartate aminotransferase level after

Table 1 Postoperative liver function of recipients in the first week after liver transplantation

	Day after operation						
	1	2	3	4	5	6	7
Serum bilirubin (µmol/l)	188 (49–384)	155 (26–311)	145 (34–404)	130 (26–396)	119 (24–353)	108 (28–305)	106 (31–363)
Serum AST (units/l)	248 (122–869)	161 (76–426)	97 (45–635)	105 (47–624)	96 (53–326)	87 (45–204)	90 (37–211)
INR	1·8 (1·5–2·3)	1·6 (1·2–2·1)	1·4 (1·1–1·9)	1·3 (1·1–1·7)	1·2 (1·0–1·5)	1·1 (1·0–1·5)	1·1 (1·0–1·5)
Platelet count (× 10^9 per litre)	62 (29–126)	45 (15–113)	51 (13–113)	49 (17–122)	65 (19–161)	71 (29–152)	96 (31–241)
Ammonia (µmol/l)	40 (1–206)	28 (1–142)	21 (6–99)	28 (7–80)	26 (3–66)	29 (25–64)	42 (18–97)

Values are median (range). AST, aspartate aminotransferase; INR, international normalized ratio donor operations (*Table 2*), although one donor had prolonged cholestasis. Her serum bilirubin level returned to normal on postoperative day 29. She was otherwise well and had no other signs of liver failure. Her liver remnant volume was 24 per cent of the total liver volume and there was no fatty change in the liver. The remnant liver volume was known before surgery. Despite the risk of postoperative liver failure, she insisted on donating the right lobe to her husband. All donors are alive at the time of writing (follow-up 6·6–33·5 (median 14·8) months).

Discussion

This study demonstrates that, in a single centre, use of LDLT with a right-lobe graft that included the middle hepatic vein had a measurable and incremental benefit over cadaveric liver transplantation for adult patients with acute liver failure. It seems, therefore, that it is appropriate to inform about the option of LDLT when interviewing patients' families for management of acute liver failure. The present study provided data that are not yet available in the literature but are important for informed consent[10].

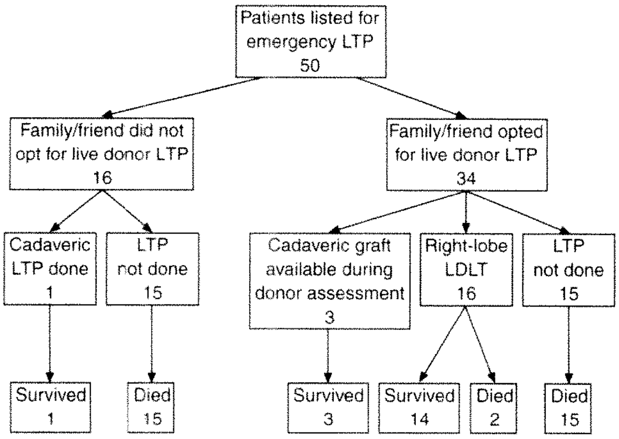
Patients listed for emergency LTP 50
Family/friend did not opt for live donor LTP 16
Family/friend opted for live donor LTP 34
Cadaveric LTP done 1
LTP not done 15
Cadaveric graft available during donor assessment 3
Right-lobe LDLT 16
LTP not done 15
Survived 1
Died 15
Survived 3
Survived 14
Died 2
Died 15

Fig. 1 Flow chart of outcome of 50 patients listed for emergency liver transplantation. LTP, liver transplantation; LDLT, live donor liver transplantation

Patients with acute liver failure have the most compelling need for liver transplantation, yet only about 10 per cent of patients could receive timely liver grafts[11]. When patients are managed in large-volume liver transplant centres, the transplant rate could be as high as 41–72 per cent[12–14], but the median waiting time for liver grafts is 5 days[14]. While waiting for a liver graft the patient might deteriorate further. Thus marginal liver grafts are not infrequently used and, together with the fact that the patient might have pretransplant multiorgan failure, the incidence of primary graft non-function is as high as 21 per cent[15] and the 1-year survival rate, 50–71 per cent[12–18], is inferior to that in patients operated for indications other than acute liver failure. Compared with cadaveric liver grafts, live donor right-lobe grafts offer distinct advantages in that patients could receive a graft relatively early and graft function is excellent because the cold ischaemia time is short. However, most live donor liver transplants in adults using a right-lobe graft are not performed in patients with acute liver failure[19–21]. In one series, right-lobe live donor liver grafts (without inclusion of the middle hepatic vein) implanted into patients with acute liver failure produced less satisfactory results[22]. The reason for this was not known, but the authors expressed concern about the adequacy of liver graft size to meet the metabolic demand of the critically ill recipient. A small-for-size liver graft is also prone to injury after reperfusion, accounting for primary graft non-function[22]. However, without inclusion of the middle hepatic vein, the right-lobe liver graft may sustain more injury because the venous outflow of the right anterior segment is occluded. In this study, with the inclusion of the middle hepatic vein in the graft, early graft function was excellent and could meet the metabolic demand of critically ill patients and even those with pre-existing chronic liver disease and portal hypertension.

The authors consider that a graft volume of 40 per cent of the estimated standard liver volume of the recipient is the

Table 2 Postoperative data for donors in the first week after donor operation

	Day after operation						
	1	2	3	4	5	6	7
Haemoglobin (g/l)	12·3 (10·7–15·8)	12·3 (9·7–15·3)	11·7 (9·5–15·3)	11·3 (9·3–13·8)	11·0 (9·6–13·6)	11·3 (9·7–13·6)	11·1 (10·0–14·2)
Platelet count (× 10^9 per litre)	211 (157–320)	173 (91–274)	172 (79–314)	193 (88–340)	194 (86–340)	193 (90–341)	215 (120–341)
INR	1·5 (1·2–2·0)	1·4 (1·2–1·9)	1·4 (1·2–1·9)	1·3 (1·1–1·8)	1·2 (1·1–1·5)	1·2 (1·1–1·4)	1·1 (1·0–1·3)
Serum bilirubin (μmol/l)	33 (13–82)	38 (17–101)	36 (23–115)	29 (15–110)	26 (12–114)	23 (11–127)	22 (13–131)
Serum AST (units/l)	200 (152–440)	183 (108–515)	139 (80–237)	83 (60–181)	83 (60–162)	91 (52–135)	77 (52–146)

Values are median (range). INR, international normalized ratio; AST, aspartate aminotransferase minimum required although Miwa *et al.*[23] achieved a 1-year survival rate of 90 per cent with a left-lobe graft (including the middle hepatic vein) that provided 35 per cent of the recipient's estimated standard liver mass. However, the duration of postoperative hospital stay and incidence of ascites were not reported. In the present authors' early experience with a left-lobe live donor graft, the patient received a graft size of 25 per cent of the estimated standard liver volume and survived, but had massive ascites for about 1 month before discharge[24]. To secure uniform success, it is considered mandatory to have a graft size of 40 per cent of the estimated standard liver volume. Compared with a left-lobe liver graft, right-lobe live donation generally meets the requirement even if the donor is smaller in body size than the recipient.

The benefit of right-lobe LDLT has to be weighed against the risk of the donor undergoing major hepatectomy. In the present series, none of the donors suffered from major complications apart from one who developed prolonged cholestasis. The pathogenesis of postoperative cholestasis is not known but was probably related to a small liver remnant. The clinical significance of postoperative cholestasis in the absence of other signs of liver failure is uncertain. It probably signified suboptimal liver function. After exclusion of bile duct injury, bile leakage, sepsis and drugs that could induce cholestasis, watchful waiting for spontaneous resolution and liver regeneration is the recommended strategy[25].

Compared with a previous report[2], the overall survival rate improved from 31 to 36 per cent. This improvement is modest because there was a large proportion of patients who could not benefit owing to lack of volunteers, delay in decision to donate, withdrawal of consent to donate and rapid deterioration of the patient's condition. Similar to cadaveric graft operations, the key to success lies in early listing and performance of liver transplantation[26]. However, it is ethically wrong to coerce families into donating organs. The decision to donate is difficult to make during the pressing moment of imminent death of the recipient. Balancing all the risks and benefits, it is important for surgeons to abstain from decision making on behalf of the families but to provide necessary information about the operations and psychological support.

In conclusion, right-lobe LDLT improves the overall survival rate of patients with acute liver failure in this locality where cadaveric organ donation is deficient. The conclusion could be extended to Western countries where cadaveric liver grafts are more abundant because timely liver grafts of adequate size and excellent function can meet the urgent demand of the critically ill patient. The addition of right-lobe LDLT to a cadaveric liver transplant programme may further improve the management of acute liver failure.

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Original article

Incidence and pattern of long saphenous vein duplication and its possible implications for recurrence after varicose vein surgery

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Background: The incidence of long saphenous vein (LSV) duplication has not been clearly established. This anomaly could have implications for recurrence after varicose vein surgery.
Methods: Some 103 saphenograms obtained in 85 patients being considered for peripheral arterial bypass surgery were reviewed. Non-ionic contrast medium was injected directly into the vein or its tributaries at the ankle. Duplications of the LSV and their relation to thigh and calf perforator veins were assessed and recorded by two independent observers.
Results: There was evidence of duplication of the LSV in 50 (49 per cent) of the 103 saphenograms. Most duplications were present in the thigh (88 per cent) and the most common pattern was a closed loop (54 per cent). Perforator veins were connected to one branch of the duplication in 42 per cent of the legs (20 per cent of all 103 legs); in half the perforator vein was connected to the non-dominant branch of the duplication. Only ten of the 18 patients who had bilateral saphenograms had duplications in both legs, and only one patient had the same pattern of duplication on both sides.
Conclusion: The incidence of LSV duplications is higher than previously reported.

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Introduction

Anatomy textbooks describe the long saphenous vein (LSV) as a continuous single trunk lying along the medial aspect of the thigh and calf receiving anterior and posterior tributaries along its course. Few reports mention the incidence and pattern of duplication or have drawn attention to the possible role of this variation as a source of recurrent varicose veins[1–4]. The LSV has an important role as autograft for arterial bypass surgery[5]. As a consequence its anatomical variations, including duplication, have received attention. The incidence of duplication has been reported to be between 1 and 52 per cent[6]. One study that used contrast saphenography to assess the LSV before bypass surgery[7] showed it connected to perforator veins in the thigh in 89 per cent of legs, but the relationship of perforators to duplications was not assessed. The authors use saphenography before femoropopliteal bypass to evaluate the LSV before operation[8].

The aim of this study was to review a consecutive cohort of saphenograms to describe the pattern and incidence of long saphenous duplications and perforator vein connections.

Materials and methods

Two independent observers reviewed 103 consecutive saphenograms performed routinely in 85 patients before bypass surgery for arterial ischaemia (*Fig. 1*). None of these patients had significant clinical varicose veins. Saphenograms were performed according to the technique described by Thomas and Posinak[9]. Sixty-seven patients had unilateral saphenography and 18 had a bilateral study. The location, configuration and length of the duplication were documented, and a note was made of differences in the symmetry of both branches (dominant *versus* non-dominant, based on their apparent diameter). A dominant vein was defined as a vein more than 1 mm in diameter larger than its fellow. The position of the perforator veins and their relationship to the duplications was also recorded. The presence of duplications and their symmetry was assessed in patients who had a bilateral study.

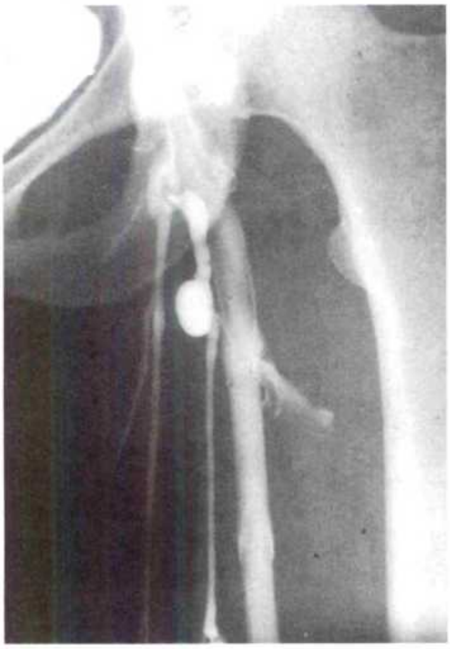

Fig. 1 Duplex long saphenous vein demonstrated on saphenography

Results

The study included 66 men and 37 women, of mean age 65 (range 38–92) years. The correlation between two observers was very good; in only two saphenograms was there disagreement and a third observer acted as an arbitrator. Fifty legs showed some form of venous duplication (49 per cent): 36 (55 per cent) of 66 men and 14 (38 per cent) of 37 women (P not significant, χ^2 test).

Configuration of the venous duplication

Thigh duplications

In 24 studies (48 per cent), duplications were confined to the thigh. The most common configuration was a closed loop, which was present in 14 of 24 legs, and a branched system was present in nine legs. Only one leg had a completely double system in which the duplication started just below the saphenofemoral junction (*Fig. 2*).

Duplications extending from thigh to calf

In 20 legs (40 per cent) the duplication extended from the thigh to the calf. A closed loop was again the most common configuration and was present in 12 legs, a branched system occurred in seven legs and one leg had a completely double vein (*Fig. 2*).

Calf duplications

Six legs (12 per cent) had a duplication localized to the calf. A branched system was present in five and one leg had a closed loop configuration (*Fig. 2*).

Triplication or meshwork

In three legs (6 per cent) the LSV consisted of a triplication or a mesh (*Fig. 3*). These three were included as duplications for the purposes of analysis.

Relationship of perforator veins to duplications

In 41 of the 50 studies that demonstrated duplications, perforator veins were seen connecting the long saphenous system to a deep vein. The perforator veins connected the duplication to the deep veins in 21 legs (42 per cent). In ten legs the perforating veins connected a non-dominant duplicated vein to the deep veins. In 13 of 21 legs the perforating vein was located in the thigh (seven at the mid-third and six in the distal third), in six legs perforator veins were present around the knee and in two the saphenous vein was connected by perforating veins to the deep veins of the calf.

Patients with a bilateral saphenogram

Eighteen patients had a bilateral study allowing 36 saphenograms to be compared. In ten of the 18 patients the LSV was duplicate in both legs; however, only one patient had the same pattern and location of the duplication in both legs.

Discussion

Duplications of the LSV are often demonstrated by dissection during arterial bypass surgery. Those who have reported that saphenous duplication is quite common have done so as part of preoperative vein assessment before arterial bypass surgery, yet there are also possible implications for recurrence after varicose vein surgery.

Phlebography (saphenography) is a reliable method of assessing variation and connections of the LSV, especially if anteroposterior and lateral images are taken[6,10]. Duplex ultrasonography is an alternative technique that is well tolerated and painless; however, it is operator dependent and may miss duplications if not performed meticulously.

It is possible that many recurrent varicose veins arise from a persistent trunk of a duplicated LSV, but this could only be confirmed by a prospective study. The presence of duplicated systems and connecting perforators would be assessed before operation, and postoperative follow-up could determine whether residual saphenous trunks con-

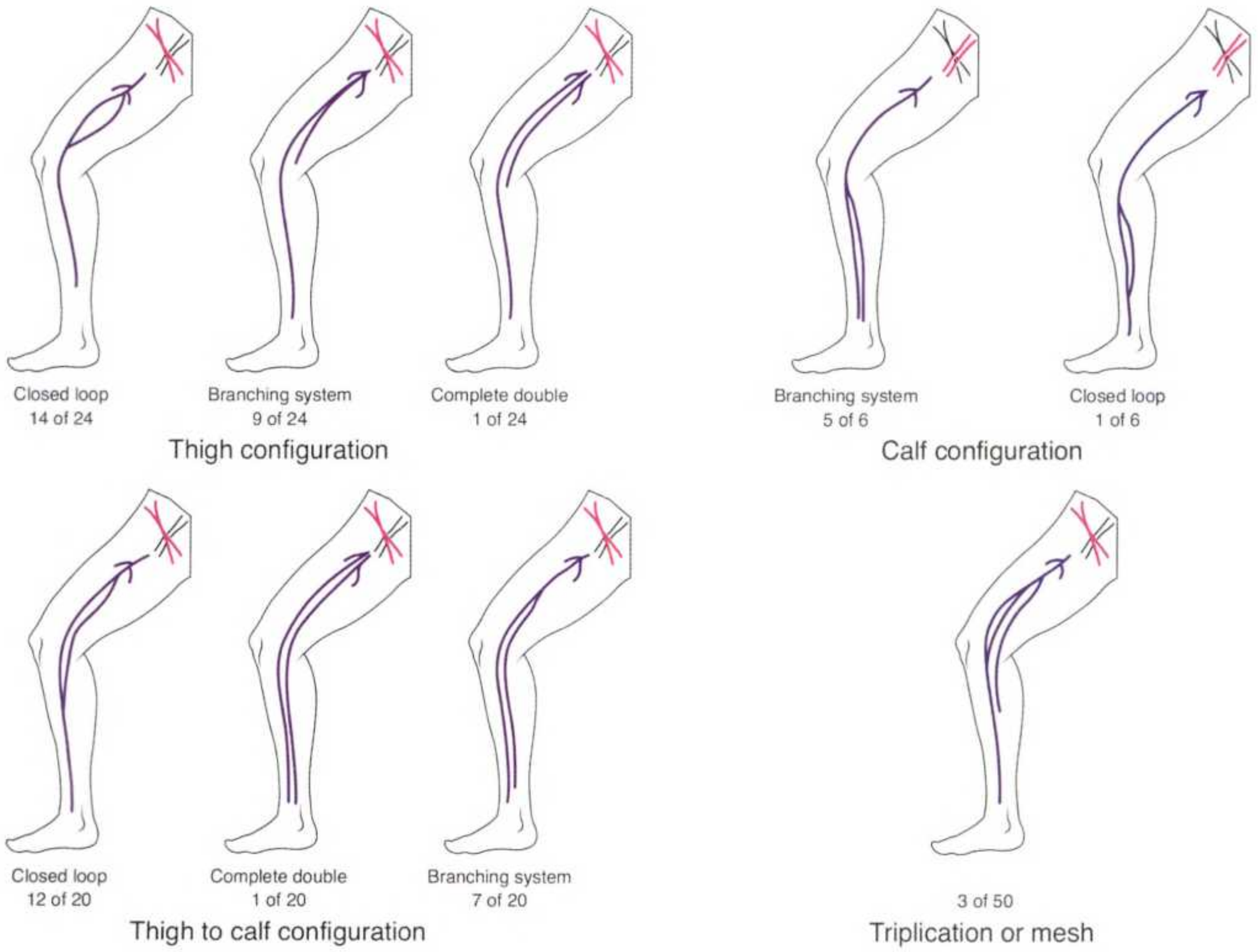

Fig. 2 Anatomical configuration of duplications of the long saphenous vein on saphenography

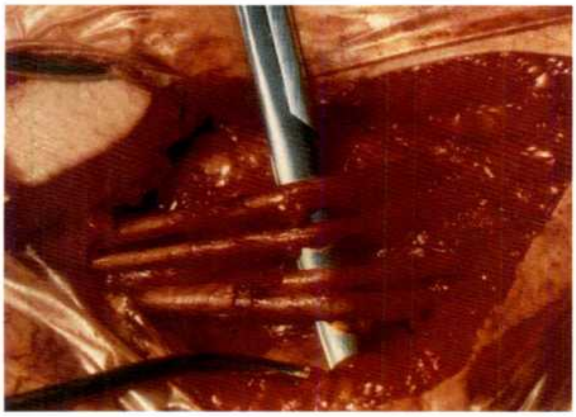

Fig. 3 Intraoperative photograph of a quadruple mesh formation of a duplex long saphenous vein

necting to perforating veins were a significant source of recurrence.

The rate of venous duplication (nearly 50 per cent) in this study is greater than the 20–30 per cent reported by others[4, 8], but similar to that reported by Shah *et al.*[6] who used saphenography and Kupinski *et al.*[11] who used duplex imaging.

A recent study using duplex imaging[12] divided LSV duplications into 'true', when the trunk lay on the deep fascia, and 'false', if one of the duplications was in the superficial fascia. While the former was rare the latter was demonstrated in 47 per cent of the scans. However, many of the 'accessory' veins described in this study were not followed to their origin and may have formed part of a duplicated system. These 'false' duplications have been included in the present study. While the separation into 'true' and 'false' seems reasonable, it is mainly a semantic exercise as the superficial vein still acts as a double system.

Only ten of the 18 patients who had a bilateral saphenogram in the present study had venous duplication in both legs and only one had the same pattern in both legs, suggesting that genetic factors have little role in determining venous anatomy.

Perforating veins connected to a non-dominant branch of a saphenous duplication in a fifth of all legs studied. Because this vein has a smaller diameter, it is less likely to accept a stripper and therefore less likely to be avulsed. This may explain the findings of Darke[13] and Stonebridge *et al.*[14] that between 35 and 40 per cent of recurrent varicose veins in the LSV distribution were due to thigh perforating veins. Either limb of a duplication, if left intact during LSV stripping, remains a potential source of recurrent varicose veins.

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Original article

Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer

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Background: Knowledge of prognostic factors following resection of rectal cancer may be used in the selection of patients for adjuvant therapy. This study examined the prognostic impact of the circumferential resection margin on local recurrence, distant metastasis and survival rates.

Methods: A national population-based rectal cancer registry included all 3319 new patients from November 1993 to August 1997. Some 686 patients underwent total mesorectal excision with a known circumferential margin. This shortest radial resection margin was measured in fixed specimens. None of the patients had adjuvant radiotherapy.

Results: Following potentially curative resection and after a median follow-up of 29 (range 14–60) months, the overall local recurrence rate was 7 per cent (46 of 686 patients): 22 per cent among patients with a positive resection margin and 5 per cent in those with a negative margin (margin greater than 1 mm). Forty per cent of patients with a positive margin developed distant metastasis, compared with 12 per cent of those with a negative margin. With decreasing circumferential margin there was an exponential increase in the rates of local recurrence, metastasis and death.

Conclusion: The circumferential margin has a significant and major prognostic impact on the rates of local recurrence, distant metastasis and survival. Information on circumferential margin is important in the selection of patients for postoperative adjuvant therapy.

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Introduction

Histopathological reporting of rectal cancer traditionally includes information on resection margins, usually the bowel resection margins. Tumour involvement of the proximal bowel margin is unusual, and distal intramural tumour extension more than 2 cm from the primary lesion is uncommon. The circumferential margin of resection has less frequently been reported but, as pointed out by Quirke *et al.*[1] and others[2–5], circumferential margin involvement appears to be a strong predictor of local recurrence and hence of survival. Others have argued that circumferential margin involvement is more an indicator of advanced disease than of incomplete excision[6]. However, from a clinical point of view, these papers[1–6] consider heterogeneous patient populations that are difficult to interpret.

The Norwegian Rectal Cancer Project was initiated in 1993. The objectives were to enhance the quality of surgery in Norway by the introduction of total mesorectal excision (TME) as the standard resection technique, to reduce local recurrence rates by operation alone, to improve survival after curative surgery, and to establish a quality control instrument with feedback to participating hospitals.

The present study examined the role of the circumferential margin and its prognostic importance for local recurrence, distant metastasis and survival in a national cohort of patients undergoing major rectal resection for cancer. Data from patients who undergo a standardized operation, and in whom the mesorectum is excised, may better reflect the potential importance of the circumferential margin and may elucidate whether circumferential margin involvement reflects advanced disease rather than

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The Editors have satisfied themselves that all authors have contributed significantly to this publication

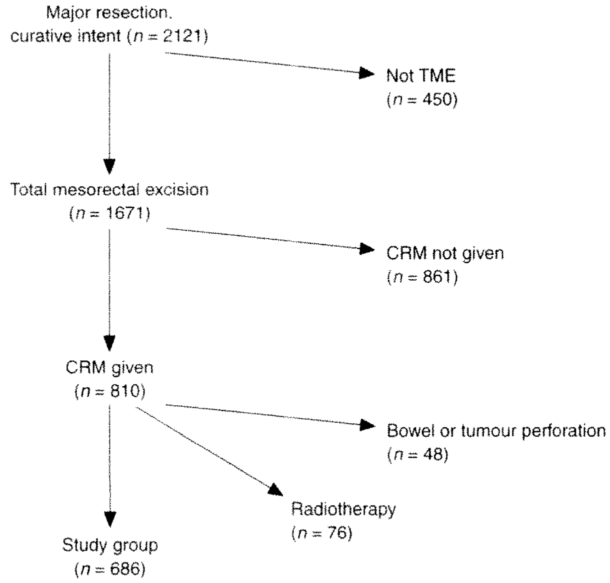

Major resection, curative intent (n = 2121)
Not TME (n = 450)
Total mesorectal excision (n = 1671)
CRM not given (n = 861)
CRM given (n = 810)
Bowel or tumour perforation (n = 48)
Radiotherapy (n = 76)
Study group (n = 686)

Fig. 1 Flow chart of the selection process for the study group. CRM, circumferential margin; TME, total mesorectal excision

incomplete excision. Finally, the information obtained may guide the selection of patients for adjuvant radiotherapy and/or chemotherapy.

Patients and methods

In a national audit, 3319 patients with rectal adenocarcinoma were diagnosed and treated in 55 hospitals (seven university, 14 district general and 34 local hospitals) in Norway from November 1993 to August 1997. TME was used in 79 per cent and a non-TME resection in 14 per cent of the operations, and the operative technique was not stated in 7 per cent.

A major rectal resection (i.e. anterior or abdominoperineal resection or a Hartmann procedure) with a curative intent was performed in 2121 patients with a tumour at or below 16 cm from the anal verge. Of these, 686 patients underwent TME, and data on the circumferential margin were available from the pathology report (*Fig. 1*). None of these patients had adjuvant radiotherapy.

Adjuvant chemotherapy was not part of the national treatment policy for rectal cancer (formulated by the Norwegian Gastrointestinal Cancer Group)[7]. However, 3 per cent of the patients had chemotherapy as they were included in a separate randomized clinical trial in the period from January 1993 to October 1996.

A disease-specific database was established in the Cancer Registry of Norway, a population-based registry with compulsory reporting of cancer. Clinical and operative data were submitted on project-specific forms, and copies of pathology reports gave additional information on staging. Follow-up was complete and facilitated by a unique national 11-digit personal identification number system. Survival data were delivered by the Norwegian Cause of Death Registry.

Before commencing the Norwegian Rectal Cancer Project, colorectal surgeons were taught the main principles of TME. To standardize rectal cancer surgery on a national level, the surgeons attended several workshops, including live video demonstrations that pinpointed important steps of the procedure, and they had the opportunity to assist a surgeon experienced in the technique.

The TME procedure was defined as sharp dissection under clear vision, with excision of the rectum and mesorectum contained within the mesorectal fascia. This does not necessarily mean an excision of the entire mesorectum down to the pelvic floor or anal canal, but the standard policy for division of the rectal tube and the mesorectum was 5 cm below the tumour.

During the first years of the national audit, pathologists were introduced to standardized handling and reporting of the operative specimen and to the use of tumour node metastasis (TNM) criteria. The pathology laboratories were encouraged to follow the quality control principles formulated by Quirke *et al.*[1,8] in their assessment of the specimens, emphasizing the role of the circumferential margin and the mesorectal lymph nodes. The fresh specimens were opened along the antimesenteric border, avoiding the tumour if possible, and fixed in formalin. Specimens were then sectioned in the transverse plane in order to identify the shortest distance (in millimetres) from the outermost part of the tumour to the lateral resection margin (*Fig. 2*). If macroscopic tumour deposits were noted in the mesorectum outside the main tumour, the measurement was made to the outer border of the deposit. In this study a circumferential margin greater than 1 mm was defined as an uninvolved margin[1].

Local recurrence was defined as recurrent disease in the pelvis, including recurrence at the site of the bowel anastomosis and of the perineal wound[9]. Metastases denote recurrent disease outside the pelvis, including metastases in para-aortic and/or inguinal lymph nodes. Local recurrence rates are given as the sum of local recurrence occurring in isolation and concomitant with distant metastasis; the rate of metastasis incorporates distant metastases with or without local recurrence. Recurrent disease was diagnosed clinically or by imaging. Histopathological or cytological verification was encouraged but not required.

The follow-up regimen adhered to the principles formulated by the Norwegian Gastrointestinal Cancer Group[7]. This regimen included clinical examination,

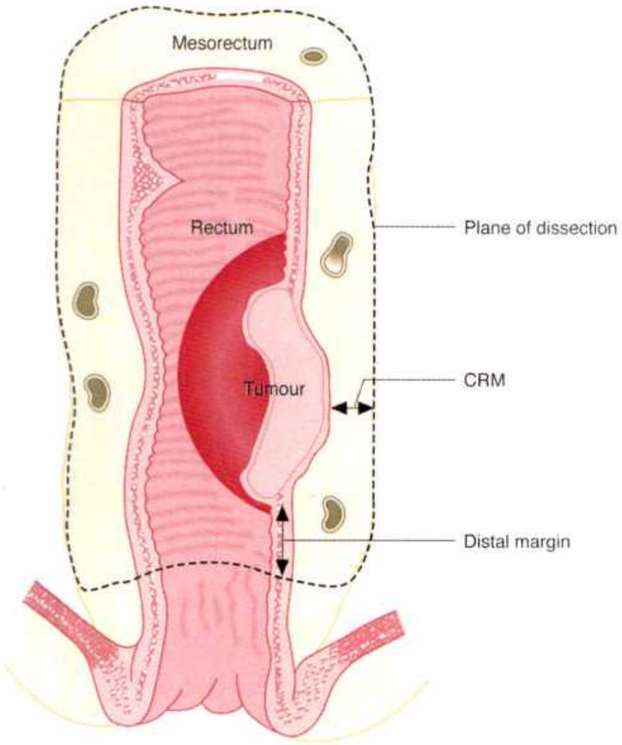


Fig. 2 Illustration of the circumferential resection margin (CRM). Redrawn with permission from the American College of Surgeons from *J Am Coll Surg* 1997; **184:** 84–92. Original illustration by Kari C. Toverud

proctoscopy, ultrasonography of the liver, chest radiography and determination of serum carcinoembryonic antigen level. The individual follow-up programme was left to the discretion of the participating hospital. Commonly, follow-up consultations were undertaken every 3 months for 2 years and then every 6 months until 5 years after operation. Median follow-up was 29 (range 14–60) months.

Statistical analysis

Patient and treatment characteristics were described using frequency tables. Missing data were included as 'not stated'. Cumulative hazard rates (HRs) of local recurrence, metastasis and crude survival were estimated by means of univariate Kaplan–Meier plots.

The importance and statistical significance of potential prognostic factors were analysed with Cox proportional hazard regression models, and significant variables were included in the final regression analyses. If one variable was significant in one of the three Cox analyses, that variable was included in the two other models. In these analyses the best prognostic group acted as reference, giving a hazard ratio greater than 1 for those at greater risk of local recurrence, metastasis or death.

The Cox analyses did not incorporate T_1 tumours, as no patient with such a tumour had a local recurrence or died, and only one patient developed metastases (if T_1 tumours were included in the analyses, the HRs for T_{2-4} tumours would not have provided any useful information). The Cox analyses were performed both with missing data as separate categories and without missing data, although similar results were produced. No interactions were identified.

The role of the circumferential margin as a predictor of local recurrence was examined further in a univariate regression model, illustrated by logarithmic curve estimation weighted by cases (i.e. circumferential margin groups with more patients counted more than those with fewer patients). How well the model fits the data is given by r^2. Sensitivity, specificity and predictive values are all time dependent, and thus they have to be judged in comparison with the median follow-up.

Statistical analyses were performed using the Statistical Package for the Social Sciences® program (SPSS, Chicago, Illinois, USA).

Results

Patient, treatment and tumour characteristics are given in *Table 1*.

The frequencies of local recurrence, metastasis and death according to circumferential margin are summarized in *Table 2*. The overall local recurrence rate was 7 per cent. Of the 65 patients with circumferential margin involvement (margin 0–1 mm), the local recurrence rate was 22 per cent (14 of 65) compared with 5 per cent (32 of 621) in the group without margin involvement (margin greater than 1 mm) ($P < 0.001$).

There were no significant differences in patient characteristics between those with information on the circumferential margin and those without ($n = 861$; *Fig. 1*). The rate of local recurrence was slightly lower (6 per cent) in the group of patients without information on the resection margin than in the study group. This difference was not statistically significant.

Cumulative local recurrence rates related to length of follow-up and circumferential margin categories are given in *Fig. 3*. The impact of the circumferential margin is further outlined in *Fig. 4*, which gives estimated local recurrence rates according to circumferential margin ($r^2 = 0.94$).

The cumulative HRs of distant metastasis and overall survival related to circumferential margin are given in *Figs 5*

Table 1 Characteristics of 686 patients undergoing total mesorectal excision for rectal cancer

	No. of patients
Median (range) age (years)	69 (48–90)
Age group (years)	
< 50	36 (5)
50–59	103 (15)
60–69	177 (26)
70–79	254 (37)
⩾ 80	116 (17)
Sex	
F	294 (43)
M	392 (57)
Tumour level (cm)	
12–16	179 (26)
6–11	310 (45)
< 6	162 (24)
Missing	35 (5)
Circumferential margin (mm)	
0–1	65 (9)
2–5	170 (25)
6–10	168 (24)
11–19	127 (19)
⩾ 20	156 (23)
Tumour status (T)	
1	32 (5)
2	166 (24)
3	452 (66)
4	36 (5)
Node status (N)	
0	426 (62)
1	177 (26)
2	83 (12)
Dukes' stage	
A	165 (24)
B	261 (38)
C	260 (38)
Type of resection	
Anterior resection	488 (71)
Abdominoperineal resection	176 (26)
Hartmann procedure	22 (3)
Differentiation	
Low	70 (10)
Moderate	544 (79)
High	43 (6)
Missing	29 (4)

Values in parentheses are percentages

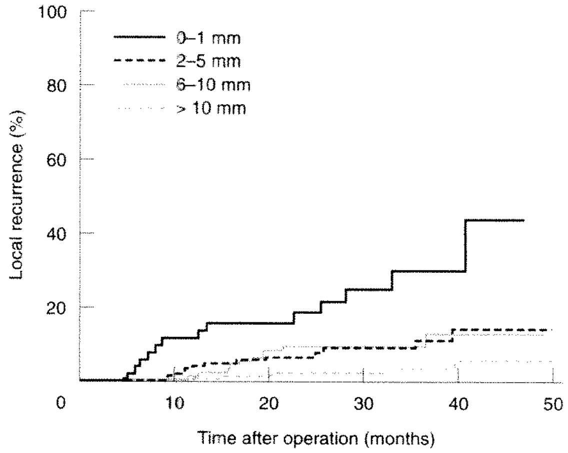
and *6*. An increasing margin was accompanied by a decrease in the proportion of patients who later developed distant metastases and by improved survival.

The prognostic impact of the circumferential margin was examined by multivariate analyses adjusted for known predictors of outcome (*Table 3*). Both circumferential margin and tumour status were found to be significant prognostic factors of local recurrence. The risk of developing local recurrence increased by a factor (HR) of 12 (95 per

Table 2 Frequency of local recurrence, metastasis and mortality according to circumferential margin

	No. of patients	Local recurrence	Metastasis	Mortality
Circumferential margin (mm)				
0–1	65	14 (22)	26 (40)	24 (37)
2–5	170	13 (8)	24 (14)	32 (19)
6–10	168	12 (7)	29 (17)	27 (16)
11–19	127	5 (4)	7 (6)	12 (9)
⩾ 20	156	2 (1)	14 (9)	10 (6)
Total	686	46 (7)	100 (15)	105 (15)

Values in parentheses are percentages



No. at risk						
0–1 mm	65	51	41	29	14	7
2–5 mm	170	152	107	64	34	7
6–10 mm	168	157	110	73	35	20
> 10 mm	283	271	204	136	70	23

Fig. 3 Local recurrence rate (cumulative hazard) according to circumferential resection margin (Kaplan–Meier analysis)

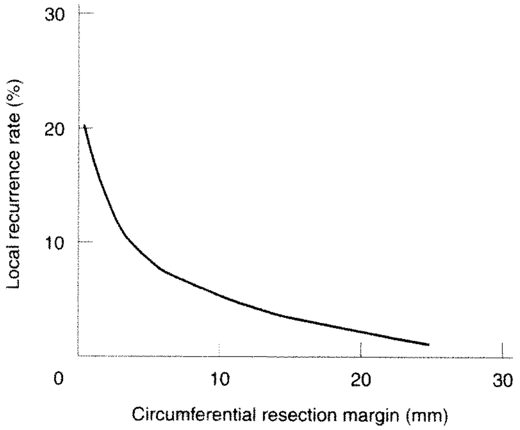
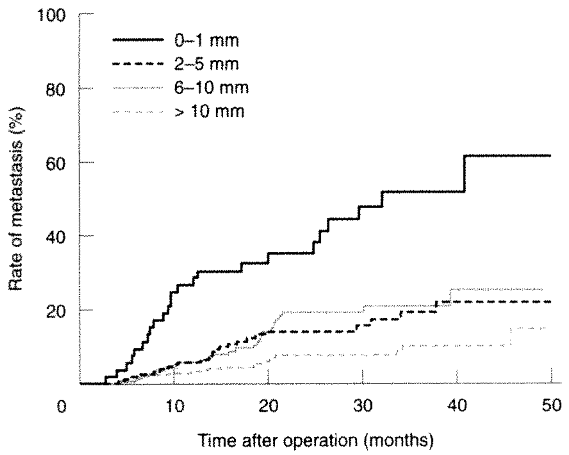
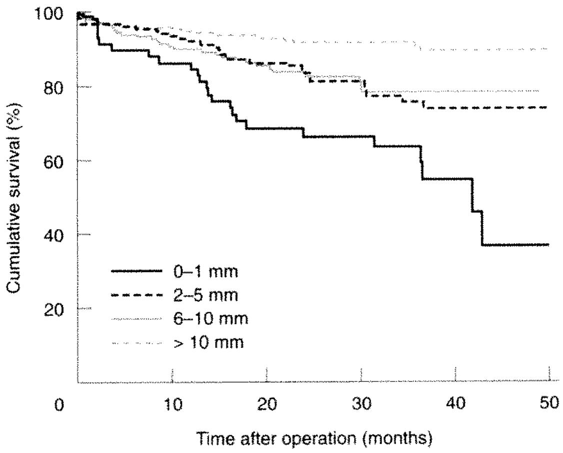


Fig. 4 Relationship between circumferential resection margin and local recurrence rate



No. at risk						
0–1 mm	65	46	32	22	11	7
2–5 mm	170	148	97	58	34	9
6–10 mm	168	156	108	70	32	17
> 10 mm	283	265	196	133	68	23

Fig. 5 Rate of metastasis (cumulative hazard) according to circumferential resection margin (Kaplan–Meier analysis)



No. at risk						
0–1 mm	65	57	42	32	16	8
2–5 mm	170	155	112	67	37	9
6–10 mm	168	158	115	75	36	20
> 10 mm	283	272	205	136	72	24

Fig. 6 Crude survival rate according to circumferential resection margin (Kaplan–Meier analysis)

cent confidence interval (c.i.) 2·6 to 55·8) when the circumferential margin was reduced from 20 to 0–1 mm. The sensitivity and specificity of circumferential margin involvement in predicting local recurrence were 30 and 92 per cent respectively, and the positive and negative predictive values were 22 and 95 per cent (*Table 4*).

Circumferential margin involvement increased the risk of developing distant metastasis significantly by a factor (HR) of 4·7 (95 per cent c.i. 2·3 to 9·5) (*Table 3*). Also the T and N statuses were significant predictors of distant metastases: N_2 status increased the risk of metastasis by a factor (HR) of 2·8 (95 per cent c.i. 1·6 to 5·0). (The low HR for the T_4 category of tumour may be explained by few T_4 tumours.) As a predictor of metastasis, circumferential margin involvement had a sensitivity and a specificity of 26 and 93 per cent respectively, and positive and negative predictive values of 40 and 88 per cent (*Table 4*), which means that 40 per cent of the patients with a positive margin developed distant metastases compared with 12 per cent of those with a negative margin.

Decreasing circumferential margin increased mortality by a factor (HR) of 3·7 (95 per cent c.i. 1·7 to 8·4) (*Table 3*). Other independent prognostic factors were tumour status, age of the patient, resection type (increased risk associated with the Hartmann procedure as a result of the selection of high-risk patients to this operation) and tumour differentiation. In prediction of mortality the circumferential margin had a sensitivity and a specificity of 23 and 93 per cent, and the positive and negative predictive values were 37 and 87 per cent respectively (*Table 4*).

Discussion

In previous publications that have addressed the issue of circumferential margin involvement, the patient populations under study were not homogeneous as some of the patients received adjuvant radiotherapy, and some studies also included palliative procedures[1,2,4,5]. Additionally, patients in whom there was intraoperative perforation of the tumour or bowel wall, a factor that would influence the prognosis negatively, were included in one study[3] and not described in others. Most previous reports were single hospital series, and thus may not have been representative of patients in general.

In the present study every patient underwent a standardized operation (TME). Other treatment-related factors of possible prognostic importance, such as preoperative radiotherapy and peroperative bowel or tumour perforation, were excluded (*Fig. 1*). The pathological examination of the specimens was performed in a routine setting, but efforts were made to standardize handling of the specimens. Thus, the present study included a patient cohort, treated for cure in a standardized clinical manner that is particularly suited to address the prognostic importance of the circumferential margin.

The frequency of circumferential margin involvement in the present study was 9 per cent (65 of 686), markedly lower

Table 3 Risk factors for local recurrence, metastasis and mortality in 654 patients undergoing total mesorectal excision for rectal cancer

	Local recurrence		Metastasis		Mortality	
	Hazard ratio	P*	Hazard ratio	P*	Hazard ratio	P*
Circumferential margin (mm)		0·01		< 0·001		0·01
≥ 20	1·0		1·0		1·0	
11–19	2·8 (0·5, 15·4)		0·7 (0·3, 1·8)		1·8 (0·8, 4·3)	
6–10	5·6 (1·2, 25·5)		2·0 (1·0, 3·8)		2·9 (1·4, 6·1)	
2–5	5·5 (1·2, 25·1)		1·5 (0·7, 3·0)		3·1 (1·5, 6·5)	
0–1	12 (2·6, 55·8)		4·7 (2·3, 9·5)		3·7 (1·7, 8·4)	
Tumour status (T)		0·05		0·04		0·02
2	1·0		1·0		1·0	
3	2·1 (0·7, 6·1)		2·0 (1·0, 4·0)		1·9 (1·0, 3·5)	
4	4·9 (1·3, 18·3)		0·9 (0·3, 2·9)		3·4 (1·4, 7·8)	
Node status (N)		0·49		< 0·001		0·71
0	1·0		1·0		1·0	
1	1·5 (0·8, 3·1)		2·1 (1·3, 3·4)		1·0 (0·6, 1·6)	
2	1·4 (0·6, 3·4)		2·8 (1·6, 5·0)		1·2 (0·7, 2·2)	
Age group (years)		0·76		0·75		< 0·001
< 50	1·0		1·0		1·0	
50–59	2·1 (0·2, 17·6)		1·2 (0·4, 3·1)		0·8 (0·2, 3·0)	
60–69	3·2 (0·4, 24·5)		1·0 (0·4, 2·8)		1·0 (0·3, 3·5)	
70–79	2·6 (0·3, 20·4)		1·1 (0·4, 2·9)		2·6 (0·8, 8·5)	
≥ 80	2·2 (0·3, 18·8)		0·7 (0·2, 2·1)		3·7 (1·1, 12·3)	
Resection type		0·17		0·65		< 0·001
Anterior resection	1·0		1·0		1·0	
APR	0·7 (0·3, 1·6)		0·8 (0·5, 1·4)		0·8 (0·5, 1·3)	
Hartmann procedure	3·3 (0·7, 15·6)		1·3 (0·3, 5·5)		4·2 (2·0, 8·6)	
Differentiation		0·29		0·20		0·002
High	1·0		1·0		1·0	
Medium	1·9 (0·2, 14·2)		1·4 (0·4, 4·6)		1·2 (0·5, 2·9)	
Low	3·4 (0·4, 28·7)		2·3 (0·6, 8·0)		3·1 (1·2, 8·1)	

Patients with T_1 tumours were not included. Values in parentheses are 95 per cent confidence intervals. APR, abdominoperineal resection. *Multivariate analysis and Cox regression

Table 4 Predictive values of circumferential margin involvement (0–1 mm) for local recurrence, metastasis and mortality in 686 patients undergoing total mesorectal excision for rectal cancer

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Local recurrence	30	92	22	95
Metastasis	26	93	40	88
Mortality	23	93	37	87

PPV, positive predictive value; NPV, negative predictive value

than that of others[1,2,4,6]. Similarly, the local recurrence rate in the whole group of patients was low (7 per cent). Consequently, the sensitivity (30 per cent) and positive predictive value (22 per cent) of circumferential margin involvement for the development of local recurrence were much lower than the values reported by Quirke *et al.*[1] and others[2]. More important, however, is the high specificity (92 per cent) and negative predictive value (95 per cent) of an uninvolved circumferential margin (greater than 1 mm). Such a level of prediction can guide clinical practice, i.e. whether to use adjuvant postoperative radiotherapy or not. Only 5 per cent of patients in the present series with an uninvolved circumferential margin developed local recurrence. Thus, if it may be assumed that radiotherapy can halve the local recurrence rate, radiotherapy would have overtreated 97 per cent of the patients.

The local recurrence rate was inversely related to the circumferential margin (*Table 2*). *Fig. 3* demonstrates that the risk increment with time is of relatively little clinical importance as long as the margin is greater than 1 mm. It is with a margin of 1 mm or less that risk increases substantially, and an exponential increase in risk is demonstrated in *Fig. 4*. This is of practical importance, as a complete excision of the mesorectum will optimize the probability of obtaining a circumferential margin greater than 1 mm even in patients with a locally advanced tumour.

The circumferential margin and tumour status influenced local recurrence significantly, while node status did not. It has been well documented by others[10–13] that node-positive patients are at higher risk of developing local recurrence. The analyses summarized in *Table 3* show, however, that the effect of node status is negated when the variable circumferential margin is introduced in the analysis. The clinical interpretation of this finding is that the circumferential dissection that characterizes TME eliminates the inherent risk of lymph node involvement as long as the margin is larger than 1 mm. This is illustrated in the group of patients with Dukes' C tumours in whom the local recurrence rate was 9 per cent if the circumferential margin was greater than 1 mm (data not shown).

The circumferential margin is also an independent risk factor for the development of distant metastases and mortality (*Table 3*). For metastases, circumferential margin involvement is a detrimental factor which increases risk exponentially, while there is a more gradual risk relationship between circumferential margin and survival (*Figs 5* and *6*).

Hall *et al.*[6] have claimed that circumferential margin involvement may reflect an advanced nature of the tumour rather than an inadequate surgical clearance. There were, however, contradictory and unexpected findings in their study. For instance, the local recurrence rate was similar in the margin-negative (11 per cent) and margin-positive (15 per cent) groups (in the present study the equivalent rates were 5 and 22 per cent). The conclusion of Hall *et al* was based on a cohort of 152 patients, compared with 686 patients in the present study, which may explain the different results.

The present data show that advanced disease (higher tumour status, more advanced node status and poor differentiation of tumour) is a significant risk factor, but of less importance than obtaining a tumour-free circumferential margin. Thus, surgeons should maximize the probability of obtaining a tumour-free margin by adopting the operative principles of TME. Of all the independent risk factors, the only one that can be manipulated by treatment is the circumferential margin.

In conclusion, this study has provided evidence that following routine TME and pathological examination of the surgical specimens for rectal cancer the circumferential margin is an important prognostic indicator of local recurrence, distant metastasis and survival. This knowledge can be used in the selection of patients for postoperative adjuvant therapy.

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Original article

Breast reconstruction in the United Kingdom and Ireland

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Background: Although it is becoming more common, previous surveys have identified concerns regarding the safety of immediate reconstruction following mastectomy. The aims of this study were to define current practice of breast reconstruction in the UK and Ireland, and to identify the characteristics of surgeons who use immediate breast reconstruction.

Methods: A postal questionnaire survey of 498 consultant breast surgeons in the UK and Ireland was performed in January 2000.

Results: There were 376 responses (response rate 76 per cent). Eighty-eight per cent of surgeons 'always' or 'usually' discuss reconstruction with patients due to undergo mastectomy; clinicians with a heavy caseload were significantly more likely to discuss it (odds ratio (OR) 18·45 (95 per cent confidence interval 1·99 to 171·07)). The majority of respondents (57 per cent) preferred delayed to immediate breast reconstruction; 70 per cent believed that immediate reconstruction has disadvantages, most commonly that it interferes with adjuvant therapy (56 per cent). Older surgeons were significantly less likely to perform immediate reconstruction (OR 5·18 (2·21 to 12·11)), and were significantly more likely to believe that immediate breast reconstruction has disadvantages (OR 2·02 (1·01 to 4·05)). Surgeons from Ireland were less likely to discuss and perform breast reconstruction (OR 0·20 (0·10 to 0·43) and 0·27 (0·12 to 0·60) respectively), or to have access to a plastic surgeon (OR 0·22 (0·11 to 0·44)).

Conclusion: Significant variation exists in the delivery of breast reconstruction after mastectomy in the UK and Ireland. The age, workload and personal characteristics of the surgeon are important in determining reconstructive practice.

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Introduction

Despite the trend towards breast-conserving surgery[1], approximately 40 per cent of patients with breast cancer still require mastectomy. Breast reconstruction after mastectomy has become more popular[2] as safe reconstructive techniques have evolved, along with increased availability of surgical expertise.

Reconstruction can be performed immediately after the mastectomy or as a delayed procedure. Previous papers have surveyed the attitudes of Australian[3], UK and Irish[4], and American[5,6] surgeons to breast reconstruction; concerns were identified that immediate breast reconstruction may compromise excision margins, interfere with adjuvant treatment or delay the diagnosis of locoregional recurrence.

In 1997, the Breast Specialty Group of the British Association of Surgical Oncology (BASO) surveyed breast and plastic surgery units in the UK and Ireland to assess caseload, case mix, timing of reconstruction, collaboration with plastic surgeons and training/teaching facilities. Although the response rate was only 48 per cent, insight was gained into existing practice. Only a minority of breast units provided a comprehensive breast reconstruction service. Most units carried out a relatively small number of breast reconstructions; only 22 per cent performed more than 50 per annum. The majority of reconstructions were delayed; only 28 per cent of units performed 75 per cent of their breast reconstructions at the time of mastectomy. Units enjoying formal links with plastic surgeons offered the most comprehensive reconstruction service.

The aims of the present study were to define the current state of breast reconstruction after mastectomy in the UK and Ireland, and to identify the personal characteristics of breast surgeons that determine the practice of immediate breast reconstruction.

Materials and methods

Database

Using a database of breast cancer services[7] every National Health Service hospital offering breast cancer surgery in the UK was telephoned and asked to supply the names of all consultant surgeons who treated breast cancer. The list of surgeons from the Republic of Ireland was compiled by M.J.K. A database of 498 surgeons was assembled: England 337, Northern Ireland 11, Wales 18, Scotland 37 and Republic of Ireland 95.

Questionnaire

A questionnaire was designed to establish information about personal characteristics, clinical workload, preoperative discussion of breast reconstruction, timing of reconstruction and reconstructive services available. The questionnaires were posted in January 2000, with a second mailing and reminder letter 1 month later. The closing date for replies was 1 April 2000.

Analysis

Statistical analysis was undertaken using Stata 7.0[8]. Associations between variables were assessed using Pearson χ^2 test and logistic regression to calculate the odds ratio (OR) and 95 per cent confidence interval (c.i.).

Results

Response to the questionnaire

Three hundred and seventy-six replies were received (response rate 76 per cent). The number of replies (response rate) from each country was: England 263 (78 per cent), Northern Ireland ten (91 per cent), Wales 16 (89 per cent), Scotland 31 (84 per cent) and Republic of Ireland 56 (59 per cent). There were 369 questionnaires returned with all or most questions answered, one returned questionnaire was sent to the incorrect address, and there were six letters. Reasons for non-completion were: not involved with breast surgery ($n = 4$) and surgeon retired ($n = 2$). The total number of responses for analysis was 368; any discrepancy between the total number of responses to each question and 368 is due to failure to respond to that particular question.

Personal characteristics

Forty per cent of respondents were aged 41–50 years ($n = 149$), with 40 per cent ($n = 146$) between 51 and 60 years, 14 per cent ($n = 51$) between 30 and 40 years of age, and 6 per cent ($n = 21$) older than 60 years. The majority of respondents were men ($n = 342$, 93 per cent).

Clinical workload

Forty-one per cent of respondents (150 of 366) treated between 101 and 200 newly diagnosed patients with breast cancer per year; 31 per cent treated 51–100 per year, and 19 per cent of surgeons estimated that they treated fewer than 51 new patients per year. Only 10 per cent reported treating more than 200 patients per year. In all, 103 consultants (28 per cent) performed more than 50 mastectomies per annum, 157 (43 per cent) between 26 and 50, and 106 (29 per cent) fewer than 26.

Preoperative discussion of reconstruction

Almost half of the respondents ($n = 172$, 47 per cent) reported that they would always discuss breast reconstruction with a woman who was fit, less than 65 years old and required a mastectomy. One hundred and forty-nine (41 per cent) would usually discuss reconstruction, while 46 (12 per cent) would sometimes, rarely, or never talk about it. The fewer breast cancers treated, the less likely was a breast surgeon to discuss reconstruction with a patient (*Table 1*). Surgeons practising in the Republic of Ireland were less likely to discuss reconstruction. Once the ORs had been adjusted for other variables there were no statistically significant associations between discussion of breast reconstruction and the surgeon's age or sex.

Timing of reconstruction

Fifty-seven per cent of respondents (189 of 331) preferred delayed to immediate breast reconstruction. Of those who preferred delayed reconstruction, the majority (78 of 186, 42 per cent) waited 10–12 months, 5 per cent (nine of 186) waited less than 4 months, 26 per cent (48 of 186) 4–6 months, 13 per cent (24 of 186) 7–9 months and 15

Table 1 Relation between discussion of breast reconstruction before operation and other variables

Variable	Rarely*	Always†	Odds ratio	Adjusted odds ratio
Country of practice				
England	21	237	1	1
Northern Ireland	2	8	0·35 (0·07, 1·78)	0·32 (0·06, 1·66)‡
Republic of Ireland	17	35	0·18 (0·09, 0·38)**	0·20 (0·10, 0·43)‡**
Scotland	4	27	0·60 (0·19, 1·87)	0·64 (0·20, 2·04)‡
Wales	2	14	0·62 (0·13, 2·91)	0·60 (0·12, 2·87)‡
No. of new patients with breast cancer per year				
0–50	18	51	1	1
51–100	14	99	2·49 (1·15, 5·42)**	1·71 (0·57, 5·12)§
101–200	12	137	4·03 (1·81, 8·95)**	8·58 (1·59, 46·18)§**
201–300	2	28	4·94 (1·07, 22·86)**	18·45 (1·99, 171·07)§**
301–400	0	4		
401–500	0	1		
No. of mastectomies performed per year				
0–25	19	87	1	1
26–50	12	145	2·64 (1·22, 5·70)**	1·11 (0·42, 2·95)¶
51–100	15	79	1·15 (0·55, 2·42)	0·10 (0·02, 0·48)¶**
101–200	0	9		

Values in parentheses are 95 per cent confidence intervals. *Includes sometimes, rarely, never; †includes always, usually. ‡Odds ratio adjusted for surgeon's age and sex; §adjusted for surgeon's age, sex, country and number of mastectomies performed per year; ¶adjusted for surgeon's age, sex, country and number of new patients with breast cancer per year. **Statistically significant ($P<0·05$, Pearson χ^2 test)

Table 2 Perceived disadvantages of immediate breast reconstruction after mastectomy

Statement	No. agreeing
Interference with adjuvant therapy	129 (56)
Significant additional burden on patients	123 (53)
Inappropriate for patients with a poor prognosis	86 (37)
High rate of complications	72 (31)
Compromises surgical excision of cancer	39 (17)
Delays diagnosis of recurrence	33 (14)
Poor cosmetic result	32 (14)
Psychological disadvantage to patients	26 (11)
More expensive	26 (11)

Values in parentheses are percentages

per cent (27 of 186) waited more than 1 year after mastectomy. Seventy per cent (234 of 336) of respondents felt that there were disadvantages to immediate breast reconstruction (*Table 2*).

Older surgeons were more likely to believe that immediate breast reconstruction has drawbacks. Once adjusted for surgeons' sex and country of practice, ORs (95 per cent c.i.) were 2·24 (1·13 to 4·45) for surgeons aged 41–50 years and 2·02 (1·01 to 4·05) for 51–60-year-old surgeons. There were no statistically significant associations between belief in disadvantages of immediate breast reconstruction and surgeon's sex, country and number of new patients with breast cancer seen per year.

Breast reconstruction

Forty per cent of respondents (146 of 365) performed breast reconstruction themselves. The commonest procedure performed was insertion of a permanent tissue expander (*Table 3*). One hundred and five surgeons (73 per cent) performed 1–25 operations per year and only 38 (27 per cent) performed more. Older surgeons were less likely to perform breast reconstruction, with OR 0·28 (0·13 to 0·57) for those aged 51–60 years and 0·22 (0·06 to 0·72) for surgeons over 60 years old. Breast surgeons who responded from the Republic of Ireland were also less likely to do a reconstruction themselves (OR 0·27 (0·12 to 0·60)). Surgeons who saw a large number of new patients with breast cancer performed more reconstructions: OR 3·09 (1·35 to 7·09) for 101–200 per year and 7·26 (2·46 to 21·44) for 201–300 new patients per annum. These ORs were adjusted for surgeon's age, sex and country of practice.

Fifty-four respondents (15 per cent) felt that plastic surgeons were not easily available for referral in their area. Surgeons in the Republic of Ireland were significantly less likely to have a local plastic surgeon (OR 0·22 (0·11 to 0·44)). Of those who felt they were available (312 of 366), 192 (62 per cent) would not routinely refer a fit woman younger than 65 years for discussion of reconstruction with a plastic surgeon. The mean(s.d.) (range) estimated percentage of fit patients under 65 years of age who received immediate breast reconstruction was 18(23) (0–100) per cent, with a further 13(16) (0–100) per cent being referred for delayed reconstruction. Patients were less likely to receive immediate reconstruction if their surgeon was between 51 and 60 years old, or practised in the Republic of Ireland (*Table 4*). Once the ORs had been adjusted for other variables there were no statistically significant associations between estimated percentage of patients receiving immediate breast reconstruction and surgeon's sex or number of new patients with breast cancer seen per year.

Discussion

Morrow *et al.*[2] have recently shown that patient factors (age, family income, tumour stage and ethnicity) are predictive of whether or not women undergo breast reconstruction after mastectomy. The present study identified the importance of surgeon factors in determining reconstructive practice.

In 1991, 58 per cent of surgeons who treated breast cancer discussed reconstruction before operation in all, or most, cases[1]. In the present study, 88 per cent of breast surgeons usually or always discussed reconstruction, according to BASO guidelines[9]. Surgeons who saw a large number of new patients with breast cancer per year were significantly more likely to discuss reconstruction. This is not unexpected, as surgeons specializing in breast disease are more likely to be aware of reconstruction and to have access to those who provide it. In contrast, Paulson *et al.*[5] surveyed 197 general surgeons in Kansas and found no significant association between surgeon's age and discussion of reconstruction once data had been adjusted for other variables.

Table 3 Types of breast reconstruction performed by breast surgeons who responded to the survey

Reconstruction	No. of operations
Permanent tissue expander	107 (74)
Latissimus dorsi flap	98 (68)
Latissimus dorsi flap plus expander	96 (67)
Temporary tissue expander and silicone prosthesis	87 (61)
Prosthesis alone	51 (36)
TRAM flap, pedicled	47 (34)
Deep inferior epigastric perforator flap	7 (5)
TRAM flap, free	5 (4)
Gluteal flap	1 (1)

Values in parentheses are percentage of respondents who performed the procedure. TRAM, transverse rectus abdominis myocutaneous

The majority of breast surgeons believe that delayed breast reconstruction is preferable, and that immediate reconstruction has disadvantages. The commonest reasons against immediate reconstruction were that it interferes with adjuvant therapy, places a significant additional burden on the patient, is inappropriate for patients with a poor prognosis, and is associated with a high complication rate. These fears have previously been identified in a similar American survey[5].

Despite these reservations, immediate breast reconstruction has not been shown to delay either adjuvant radiotherapy or chemotherapy[10–12]. Chemotherapy does not increase wound complication rates after immediate reconstruction[10] and immediate reconstruction has a similar rate of postoperative wound complications to modified radical mastectomy alone[13]. There is evidence that immediate breast reconstruction improves psychological outcome[14] and is associated with significantly less psychosocial and psychological morbidity[15,16]. However, a recent study produced conflicting results[17]. There was no significant difference in recurrence rates between women who had immediate breast reconstruction and those who did

Table 4 Association between estimated percentage of patients who received immediate breast reconstruction after mastectomy and other variables

Variable	< 10 per cent	≥10 per cent	Odds ratio	Adjusted odds ratio
Age of surgeon (years)				
30–40	11	35	1	1
41–50	58	77	2·40 (1·12, 5·12)‡	2·05 (0·89, 4·74)*
51–60	82	44	5·93 (2·74, 12·81)‡	5·18 (2·21, 12·11)*‡
> 60	9	11	2·60 (0·86, 7·91)	2·43 (0·74, 7·94)*
Country of practice				
England	104	135	1	1
Northern Ireland	6	3	2·60 (0·63, 10·63)	2·98 (0·70, 12·69)†
Republic of Ireland	34	3	14·71 (4·40, 49·23)‡	14·35 (4·19, 49·12)†‡
Scotland	13	15	1·12 (0·51, 2·47)	1·15 (0·49, 2·69)†
Wales	4	11	0·47 (0·15, 1·52)	0·48 (0·14, 1·63)†

Values in parentheses are 95 per cent confidence intervals. *Odds ratio adjusted for surgeon's sex and country of practice; †adjusted for surgeon's age and sex. ‡Statistically significant ($P<0·05$, Pearson χ^2 test) not[12,18]. A 1995 survey[4] showed that 34 per cent of surgeons were concerned that reconstruction may mask local recurrence; this view is now less common.

The present study demonstrated an improvement in reconstructive services when compared with the 1997 BASO survey. A significant minority of breast surgeons now perform reconstructions themselves; just under three-quarters of these performed fewer than 25 operations per year. This caseload is low, as these operations are demanding, and flap or prosthesis failure can be disastrous. Surgeons with a high caseload were significantly more likely to perform breast reconstructions themselves. Younger surgeons were more likely to undertake breast reconstruction. This is not surprising as surgeons in large referral centres may have a specialty interest in reconstructive techniques whereas older surgeons were more likely to have trained as general surgeons. A significant minority of respondents felt that plastic surgeons were not available in their area, suggesting that improvements in reconstructive services are necessary.

Morrow *et al.*[2] showed in their analysis of over 200 000 patient records from the North American National Cancer Database that there was a significant variation in the volume of breast reconstructive surgery, similar to the geographical variation found in the present study. Surgeons practising in Ireland were significantly less likely to discuss breast reconstruction before operation, perform reconstructions themselves, have patients who received immediate breast reconstruction or have access to plastic surgical services. The validity of these results is unclear as the Irish response rate was substantially lower than that in the UK. The consistency of the association suggests that immediate reconstruction is an underutilized technique in Ireland. The publication of the Irish National Cancer Forum report suggests that these practices will change in the future[19].

Other researchers have demonstrated a lack of consensus on the management of breast cancer in south-east England[20] and Italy[21]. A similar situation exists for breast reconstruction after mastectomy in the UK and Ireland. The surgeon's age, sex, workload and country of practice significantly influenced reconstructive practice. Breast surgeons may benefit from improved awareness of immediate breast reconstruction and training in the therapeutic options available. Additional funding is needed to improve surgical expertise and allow clear lines of referral to develop.

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Original article

Late results of selective axillary surgery based on contact cytology in women with operable breast cancer

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Background: Interest in the possibility of intraoperative analysis of sentinel lymph nodes to select patients with operable breast cancer for immediate axillary clearance encouraged this review of a long-term experience of selective axillary surgery based on intraoperative contact cytology of conventionally sampled nodes. Survival was assessed as a potential marker for understaging.

Methods: Records of 437 patients who had surgery between 1991 and 1994 were reviewed to compare rates of axillary recurrence in patients who had contact cytology only with those who had contact cytology and axillary clearance.

Results: Axillary recurrence occurred in seven (3 per cent) of 219 patients who had negative contact cytology, three (4 per cent) of 75 patients who had positive contact cytology with axillary clearance and one (1 per cent) of 93 who had axillary clearance alone. In patients with positive contact cytology, 131 (78 per cent) of 168 positive nodes were in the sample specimen, which included all positive nodes on 19 occasions. Survival probability at 36, 72 and 96 months was 92, 87 and 84 per cent respectively for patients with negative contact cytology, and 85, 73 and 71 per cent for patients with positive cytology and axillary clearance.

Conclusion: A selective approach to axillary surgery based on intraoperative contact cytology of sampled lymph nodes gave good long-term control of axillary disease.

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Introduction

Selection of patients with operable breast cancer for axillary node sampling alone or immediate axillary clearance is feasible, based on intraoperative contact cytology of sampled nodes, with good short-term results[1,2]. The technique has not been widely adopted; most surgeons opt for either sampling with delayed management of the axilla[3] or routine axillary clearance for all patients[4]. The two latter approaches have been shown to be equal in a randomized clinical trial[5]. With the widespread adoption of sentinel node biopsy there has been a reawakening of interest in a selective approach to axillary surgery[6,7]. In the present study a cohort of patients who had selective axillary surgery for breast cancer based on intraoperative contact cytology between January 1991 and December 1994 was reviewed to determine the long-term rates of axillary recurrence. Survival was also assessed because this could be a marker for understaging.

Patients and methods

Clinical records of all patients with potentially operable invasive breast cancer (T_{1-3}, $N_{1a,b}$) treated from 1991 to 1994 inclusive were reviewed. A representative sample was validated by cross-checking. This interval was chosen in order to give adequate follow-up. It also coincided with the adoption of a policy of giving adjuvant medical therapy to all patients with a Nottingham Prognostic Index (NPI)[8] score of 3 or more, ensuring that all patients were treated consistently according to protocol, the only variable being the management of the axilla.

A previously described method of axillary sampling was employed[1,2]. Briefly, this involved palpation of the whole axillary contents; four hard and/or enlarged nodes were selected for immediate contact cytology. Nodes were taken to the pathologist by the surgeon, bisected and the two halves dabbed on to microscope slides, dried, stained with haematoxylin and eosin, and assessed immediately. Patients with positive cytology had immediate level 3 axillary clearance. Sampling was carried out by the senior surgeon or by a specialist registrar under supervision. Contact cytology was performed by a consultant pathologist or a supervised trainee. All sampled nodes were subsequently submitted to paraffin-section histology. In six cases, the histology was positive on one cytology-negative sampled node. A policy of surveillance was adopted because a pilot study had shown that no further positive nodes were likely to be found if only one node was discordant[1]. Patients who had breast conservation surgery subsequently had radiotherapy to the remainder of the breast but axillary radiotherapy was not employed. All patients with a NPI score of more than 3 received adjuvant chemotherapy or tamoxifen according to age and menopausal status.

Results

There were 437 patients in the interval under review; 50 had surgery elsewhere or had incomplete records. Some 387 underwent the complete protocol. The mean age of the patients was 58 (range 23–88) years, and the mean tumour size was 22·3 (range 2·0–90·0) mm. Some 58 per cent of women had breast conservation and 42 per cent had a mastectomy. A total of 219 patients had contact cytology only, 75 had cytology followed by axillary clearance and 93 had axillary clearance only, either because of obvious axillary disease or lack of theatre or pathology time for contact cytology (up to 30 min per case) at the end of the operating day.

A mean of 4 (range 1–8) nodes was sampled from each patient. Axillary clearance specimens yielded a mean of 12 (range 2–36) nodes, and the mean number of positive nodes was 2 (range 0–30) per patient.

In patients who had positive cytology and axillary clearance, 131 (78 per cent) of 168 positive nodes were in the sampled specimen, and in 19 instances the sampled nodes included all the positive nodes.

Axillary recurrence

Axillary recurrence occurred in seven (3 per cent) of 219 patients with negative contact cytology, three (4 per cent) of 75 patients who had positive contact cytology and axillary clearance, and one (1 per cent) of 93 patients who had axillary clearance only. There was no statistically significant difference between the groups. Five patients with axillary recurrence died during follow-up; three had axillary clearance for positive cytology as initial treatment. In one, axillary recurrence occurred 11 months after supraclavicular recurrence. In the other two, axillary recurrence preceded visceral recurrence by 19 and 27 months. Of the seven patients with axillary recurrence after negative cytology, the mean interval to recurrence was 36 (range 1–77) months. All subsequently underwent axillary clearance. Five are alive and disease free 1–43 months after this event. Two died 8 and 14 months after axillary recurrence. Supraclavicular node recurrence occurred in none of 219 patients with negative cytology and in three of 75 patients with positive cytology who had axillary clearance, an incidence too low to justify statistical analysis.

In 14 patients there was discordance between node cytology and subsequent histology. Eight patients had positive cytology but negative histology. These were regarded as node positive for treatment purposes. Six patients with negative cytology had one positive node on histology. None had axillary clearance or radiotherapy to the axilla, but all had adjuvant medical therapy and five remain disease free. One developed simultaneous axillary and liver secondaries, and died within 9 months from brain secondaries.

Kaplan–Meier survival estimates in patients who had negative contact cytology were 92 per cent at 36 months, 87 per cent at 72 months and 84 per cent at 96 months. Respective values in patients who had axillary clearance for positive cytology were 85, 73 and 71 per cent.

Discussion

Axillary node sampling is widely practised; 35 per cent of cancers are treated by this method in some areas of the UK[9]. A recent randomized trial has shown outcomes to be similar for both sampling and routine axillary clearance[5]. The technique of intraoperative analysis of sampled nodes to help select axillary treatment has not been adopted widely, even though good early outcomes have been reported[1,2]. The present study concerned long-term results obtained from intraoperative contact cytology. Major concerns about this selective approach to axillary clearance are the possibility of local recurrence in the axilla and a survival disadvantage owing to understaging and subsequent failure to give adjuvant medical therapy.

The present study was small and uncontrolled so a definitive statement about survival effects of the technique cannot be made. However, the survival probabilities for patients with negative cytology were within the range of other published studies[10,11]. The survival figures had value only as a marker for possible disadvantage resulting from understaging. Within these limitations, the figures were consistent with the hypothesis that the method did distinguish adequately between node-negative and node-positive women.

The problem of understaging and selection for adjuvant medical treatment is less important now that factors other than node status are considered, as in the NPI. Recently all patients with a score of 3 or above received adjuvant medical therapy so that any node-positive tumour was treated, as well as any grade 2 or 3 tumour, even if node negative. Intraoperative contact cytology was used only to select patients for immediate axillary clearance. Patients with negative cytology but positive histology were regarded as false negatives for the cytology technique. In this group of patients none had more than one discordant positive node on histology, so none was submitted to completion axillary clearance. Women with positive cytology but negative nodes on histology were accepted as true positives for the purpose of staging. All were reviewed by an independent pathologist. Contact cytology consistently detected groups of malignant cells in sampled nodes (usually in small clumps in peripheral sinuses) that could not be confirmed by subsequent histological examination. Whether more discordance would have been discovered if the nodes had been subjected to the intensive histological techniques being investigated in relation to sentinel node biopsy is a matter for conjecture[12]. The advantages of a selective approach are obvious. Breast conservation surgery with node sampling alone can be performed with an overnight stay only. Axillary clearance requires prolonged care of drains in hospital or specialist nursing care at home. With the technique described, up to 74 per cent of patients were spared immediate axillary clearance at the first operation while only 3 per cent of these required a later axillary operation for local control. A much larger study would be required to see whether this resulted in a survival advantage, and would have to include cost-effectiveness and quality of life measures.

As sentinel node biopsy becomes widely accepted, surgeons may be encouraged to adopt a selective approach to axillary surgery because of the precision of the method. However, the accuracy of the technique has been shown to be variable in multicentre studies[13,14] in which the number of sentinel nodes removed ranged from one to eight. In this study the high proportion of positive nodes included in the sampled nodes and the number of women in whom the only positive nodes were in the sample suggests that a positive sentinel node will probably be included in a carefully performed sample[15]. In centres without radioisotope facilities surgeons might like to consider whether this technique might give equally good results to sentinel node biopsy.

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Original article

Surgical workload and outcome after resection for carcinoma of the oesophagus and cardia

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Background: Performing cancer surgery in high-volume centres may lead to improved outcomes. This study explored the relationship between annual workload and outcome following resection for carcinoma of the oesophagus and cardia.

Methods: The study was a retrospective case-note review of 1125 patients who had surgery for cardio-oesophageal cancer in the West Midlands region of England. Outcome measures were 30-day mortality and long-term survival.

Results: The overall 30-day mortality rate was 10·0 per cent with a median survival of 14 months and a 5-year survival rate of 17·2 per cent. Increasing age, advanced stage of disease and emergency resection independently affected outcome adversely. Forty-one infrequent operators (fewer than four resections per year) performed 146 resections (13·0 per cent), 18 intermediate operators (between four and 11 resections per year) performed 488 resections (43·4 per cent) and five frequent operators (12 or more resections per year) performed 491 resections (43·6 per cent). The 30-day mortality rate was greatest in the infrequent group (15·1 per cent) compared with both the intermediate group (6·6 per cent; adjusted odds 0·40, $P = 0·004$) and the frequent group (11·8 per cent; odds 0·73, $P = 0·28$). There were no differences in survival rates between the groups, and no difference in outcome between high- and low-volume hospitals.

Conclusion: In this unselected population-based series there was little evidence of a trend of improving 30-day mortality rate with increasing workload, or between workload and long-term survival.

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Introduction

A major aim of the modern National Health Service in the UK is to improve the outcome after cancer treatment[1]. It is hoped that the establishment of multidisciplinary teams and cancer networks, together with the development of national guidance for purchasers[2], will improve the quality of cancer care. It seems logical that concentration of cancer therapy should lead to improved outcomes.

Cancer of the oesophagus and gastric cardia has a poor outlook, largely because of its late presentation in predominantly elderly patients. In the minority of patients who are suitable for surgical resection there has been much debate on whether specialization and increasing the volume of workload may improve outcomes.

The aim of this study was to assess the current outcomes from surgery for cardio-oesophageal cancer in a UK region, with particular respect to the effect of individual surgeon and hospital workload.

Patients and methods

All patients in the West Midlands region (population 5·3 million) diagnosed with carcinoma of the oesophagus or cardia between 1992 and 1996 were studied retrospectively. Approval was secured from all local and regional ethics committees for the first author to retrieve and study all available case notes.

Patients were identified from hospital information and coding systems, local clinical, surgical and endoscopy databases, and histopathology records, together with information held centrally at the West Midlands Regional Cancer Intelligence Unit (CIU). A standard data capture form was used to collect basic patient demographics together with clinical and pathological features of the disease presentation, management and progress. Survival data were augmented by reference to local general practitioners and central death records.

A total of 4114 case notes was reviewed, from which 3660 patients were identified with a malignant neoplasm of the oesophagus or cardia. Only 125 (3·4 per cent) of the case records were not available from any source. Some 1132 patients (30·9 per cent) underwent surgical resection; seven patients were excluded because the operation was performed outside the region. For the 1125 patients studied, data were retrieved from full hospital notes for 945 patients (84·0 per cent) and from the abbreviated CIU notes only in 180 (16·0 per cent). Hospital notes were unavailable for various reasons, including being simply lost from central files, deliberately destroyed, or incarcerated in asbestos-lined storerooms or warehouses that had been flooded.

CIU notes did not contain the date of discharge from hospital, so in-hospital mortality could not be recorded for all cases. Outcome from surgery was therefore measured as 30-day mortality and long-term survival. Follow-up for survival was largely complete to 5 years. It was lacking in only 56 patients, most of whom were treated in 1996. Patient factors assessed included age, disease site, histological type, stage, American Society of Anesthesiologists (ASA) grade, smoking habit, whether preoperative chemotherapy was administered, the surgical operation performed, and whether the resection was an emergency or elective operation, or palliative or potentially curative. A potentially curative operation was defined as one where the specimen had histologically clear proximal, distal and lateral margins, and there were no distant metastases, N_2 nodal involvement or invasion into adjacent organs. ASA grading and smoking habit data were incomplete owing to the retrospective nature of the data collection.

Surgical workload was analysed for each individual surgeon by the mean number of operations performed per year. The mean number of resections performed was determined by the number of years in post during the 5-year interval. Surgeons were divided arbitrarily into three groups: an infrequent operation group in which surgeons performed fewer than one operation every 3 months (fewer than four resections per year), an intermediate operation group in which between four and 11 resections per year were performed, and a frequent operation group in which 12 or more resections per year were carried out. Hospitals were grouped arbitrarily into low- and high-volume units (fewer than, or more than, 20 resections per year).

Statistical analysis

Pearson and Mantel–Haenszel χ^2 tests for linear association were used to test differences in 30-day mortality between the groups. Kaplan–Meier survival rates were estimated and survival curves were compared by means of log rank methods. Logistic regression was used to identify predictors of 30-day mortality and thereby to estimate adjusted odds ratios. Cox's proportional hazards model was used to identify predictors of survival, and to estimate adjusted ratios for risk of death.

Results

Of 1125 patients who underwent cardio-oesophageal resection, 798 (70·9 per cent) were men and 327 (29·1 per cent) were women. Their median age was 66 (range 20–87) years. The distribution by histological type and site is shown in *Table 1*. Seventy-one patients (6·3 per cent) had stage 1 oesophageal cancer, 357 (31·7 per cent) had stage 2, 564 (50·1 per cent) had stage 3 and 133 (11·8 per cent) had stage 4 disease.

The overall outcome results for all the patients are summarized in *Table 2*. The 30-day mortality rate was significantly increased in patients having emergency resection (P = 0·005), in patients aged over 70 years (P = 0·001), and in those for whom full hospital notes were not found (P = 0·01). Patients whose operation was done by a surgeon who performed fewer than four such resections per year had the highest 30-day mortality rate, but the rate for the intermediate group was the lowest (P = 0·02 for differences between the three groups).

Table 1 Site and type of 1125 cardio-oesophageal malignancies

	Oesophagus			
	Upper third	Middle third	Lower third	Cardia
Squamous cell carcinoma	13 (92·9)	174 (94·6)	99 (21·7)	10 (2·1)
Adenocarcinoma	0 (0·0)	2 (1·1)	343 (75·2)	449 (95·3)
Other	1 (7·1)	8 (4·3)	14 (3·1)	12 (2·5)
Total	14	184	456	471

Values in parentheses are percentages

Table 2 Clinical outcome data for 1125 patients who had resection of carcinoma of the oesophagus and cardia

	No. of patients*	30-day mortality rate (%)	Median survival (months)†
All resections	1125	10·0	14 (13, 14)
Oesophagus	654 (58·1)	10·9	13 (11, 14)
Cardia	471 (41·9)	8·7	14 (13, 16)
Men	798 (70·9)	9·4	13 (12, 14)
Women	327 (29·1)	11·3	14 (13, 17)
Stage 1	71 (6·3)	7·0	> 60
Stage 2	357 (31·7)	10·4	24 (18, 29)
Stage 3	564 (50·1)	9·4	12 (11, 13)
Stage 4	133 (11·8)	12·8	7 (6, 8)
Elective resection	1009 (89·7)	8·9	14 (13, 15)
Emergency resection	47 (4·2)	21·3	8 (4, 16)
Not known	69 (6·1)	17·4	9 (7, 13)
Squamous cell carcinoma	296 (26·3)	10·8	13 (11, 15)
Adenocarcinoma	794 (70·6)	9·7	14 (13, 15)
Other	35 (3·1)	8·6	15 (11, 44)
Preop. chemotherapy	93 (8·3)	9·7	17 (13, 23)
No preop. chemotherapy	1032 (91·7)	10·0	13 (12, 14)
Operative status curative	767 (68·2)	9·3	18 (16, 21)
Operative status palliative	358 (31·8)	11·5	8 (7, 10)
Hospital notes available	945 (84·0)	9·0	14 (13, 15)
CIU information only	180 (16·0)	15·0	12 (9, 14)
Age < 50 years	103 (9·2)	1·9	21 (13, 28)
Age 50–59 years	261 (23·2)	4·2	15 (14, 17)
Age 60–69 years	389 (34·6)	9·8	14 (12, 16)
Age ≥ 70 years	372 (33·1)	16·4	10 (8, 12)
Infrequent operator (< 4 per year)	146 (13·0)	15·1	12 (9, 14)
Intermediate operator (4–11 per year)	488 (43·4)	6·6	15 (13, 16)
Frequent operator (> 12 per year)	491 (43·6)	11·8	13 (11, 14)
Low-volume unit (< 20 per year)	550 (48·9)	9·8	13 (12, 15)
High-volume unit (> 20 per year)	531 (47·2)	10·2	13 (12, 15)
Other (private unit)	44 (3·9)	9·1	18 (10, 40)

Values in parentheses are *percentages and †95 per cent confidence intervals. CIU, Regional Cancer Intelligence Unit

Table 3 Patient characteristics according to surgeon workload

	Infrequent (< 4 per year) (n = 146)	Intermediate (4–11 per year) (n = 488)	Frequent (≥ 12 per year) (n = 491)
No. of men	109 (74·7)	357 (73·2)	331 (67·4)
Mean age (years)	63·8	62·8	64·9
Oesophageal tumours	70 (47·9)	273 (56·0)	311 (63·3)
Preop. chemotherapy	1 (0·7)	28 (5·7)	64 (13·0)
Emergency resection*	6 (4·5)	13 (2·7)	28 (6·1)
Curative resection	86 (58·9)	337 (69·1)	343 (69·9)
Stages 3 and 4	99 (67·8)	298 (61·1)	299 (60·9)
CIU information only	24 (16·4)	61 (12·5)	95 (19·3)
Mean no. of nodes retrieved	7·1	7·4	6·9

*In 69 patients (14, 23 and 32 respectively) information on type of resection was not available. CIU, Regional Cancer Intelligence Unit

Table 3 shows the patient characteristics according to surgeon workload. The surgeons who performed operations infrequently had more advanced stage and palliative resections, whereas those in the frequent operation group had more oesophageal patients and ordered more preoperative chemotherapy. There was no difference in the number of lymph nodes retrieved by surgeons in the three groups.

In 900 operations the exact surgical procedure was recorded, of which 461 (51·2 per cent) were Lewis–Tanner resections, being equally distributed amongst the surgeon-workload groups. The surgeons in the infrequent operation group used a thoracoabdominal approach only in 20·7 per cent (24 of 116) of operations, compared with 5·8 per cent (24 of 415) in the intermediate operation group and 5·7 per cent (21 of 369) in the frequent operation group. A neck anastomosis, combined with a left thoracic or left thoracoabdominal approach, was more common in the intermediate (102 of 415 (24·6 per cent)) and frequent (115 of 369 (31·2 per cent)) operation groups than in the infrequent group (four of 116 (3·4 per cent)).

Surgeons and hospitals that performed fewer than two resections per year had the highest 30-day mortality rates (*Table 4*).

Many of the variables were related to 5-year survival, the most important being stage and age. There were no striking survival differences between surgeon-workload groups (*Fig. 1*). The overall 5-year survival rate was 17·2 per cent.

Table 4 Thirty-day mortality rate by number of cardio-oesophageal resections performed per year

No. of resections per year	No. of surgeons	No. of hospitals	No. of resections	30-day mortality rate (%)
0 to < 1	30	—	46	21·7
1 to < 2	8	—	60	15·0
2 to < 3	2	—	25	4·0
3 to < 4	1	—	15	13·3
4 to < 5	3	—	34	8·8
5 to < 6	3	—	54	13·0
6 to < 7	3	—	62	4·8
7 to < 8	3	—	78	10·3
8 to < 9	1	—	25	8·0
9 to < 10	2	—	91	4·4
10 to < 11	2	—	85	4·7
11 to < 12	1	—	59	1·7
12 to < 13	1	—	63	17·5
14 to < 15	1	—	71	12·7
16 to < 17	1	—	70	15·7
28 to < 29	1	—	141	6·4
33 to < 34	1	—	146	12·3
< 2	—	5	21	23·8
5–8	—	7	226	8·4
11–19	—	4	298	10·7
> 20	—	3	531	10·2

Factors affecting outcome

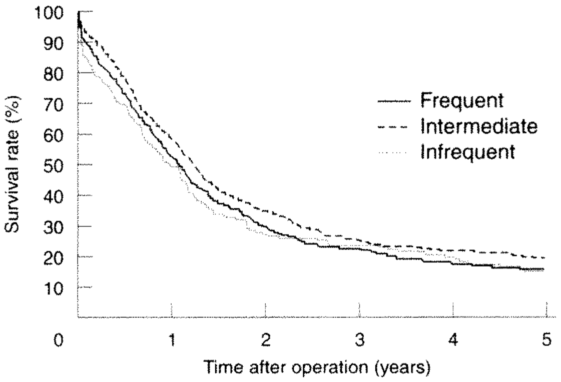
Logistic regression analysis was used to identify which patient- and disease-related variables were independently related to operative mortality. Advanced age and emergency resection were the only factors that had a clear independent effect on 30-day mortality. After adjusting for these, the intermediate operation group of surgeons achieved the lowest mortality rates, with adjusted odds of death of 0·40 (P = 0·004) compared with surgeons in the infrequent operation group. Surgeons in the frequent operation group had an odds ratio of 0·73, but this was not statistically significant (P = 0·28) in comparison with the infrequent operation group.

Factors that influenced long-term survival were analysed using Cox's proportional hazards model. Those that had a significant effect were palliative operation (risk ratio for death 1·59), stage of disease (1·87 per level), age (1·02 per year) and emergency resection (1·65) There was no evidence of any difference in long-term survival between the surgical-workload groups, the adjusted risk ratio being close to 1·0 in each group.

Discussion

This study, in an unselected group of patients across a large region of England and Wales, has shown operative mortality and long-term survival rates following resection of the oesophagus comparable with those in other Western series. It failed to identify a clear improvement in surgical outcome with increasing annual surgeon workload.

Patient- and disease-related variables, such as the age of the patient and the stage of disease, were more likely to predict the outcome from surgical resection than the annual



No. at risk

	0	1	2	3	4	5
Frequent	491	259	147	111	78	52
Intermediate	488	285	170	123	95	59
Infrequent	146	72	40	35	28	19

Fig. 1 Five-year survival after oesophageal resection according to surgeon workload. χ^2 = 5·21, 2 d.f., P = 0·08 (log rank test)

workload of the surgeon. The selection of patients for oesophageal resection has an impact on operative mortality rates[3]; mortality has improved markedly over the past 30 years[3–6]. Reports from single centres suggesting that increased volume leads to decreased mortality may be difficult to extrapolate to populations as a whole.

The relative number of operations per surgeon is higher in the UK than in North America[7], where most volume and outcome studies have been undertaken. The common theme from these reports is the very low operative mortality rates achieved in high-volume units[8–11]. As in the present study, arbitrary groupings of workload for either hospital or individual surgeons are reported. Hospital volume, as the unit of analysis for oesophageal resection, supports a volume–outcome relationship in American studies[8–10] with striking operative mortality differences between high- and low-volume hospitals. These studies are largely selected series, based on either age, type of institution, and means of insurance or healthcare payment. In the Netherlands a similar inverse relationship between hospital volume and hospital mortality rate has been demonstrated[11].

In contrast, the present study did not find an inverse relationship between increasing surgeon volume and operative mortality. There was no predominance of adverse patient factors in the frequent-operation surgeon group. Surgeons with low-, medium- and high-volume workloads achieved similar, and variable, mortality rates. This may reflect local resources and support as much as surgical expertise. Based on these data, increasing the number of annual resections above two per surgeon did not appear to confer any improvement in outcome.

The mortality rate was higher and long-term survival worse in the 16·0 per cent of patients whose full hospital notes were not available for review. If this study had included only the patients with hospital notes, it would have underestimated the true outcome from the disease. This study examined 30-day rather than in-hospital mortality because it was not possible to retrieve all the hospital notes. This problem of failure to retrieve notes in ongoing quality assurance is well known[12] and supports the need for prospective, accurate collection of data to enable comparison of treatment and outcome in whole populations[2].

Operation for cardio-oesophageal cancer is but one part of the whole management of the disease. The depressing long-term outcome is unlikely to improve unless there are changes in oncological approaches together with earlier stage diagnosis.

The motives for centralization of surgical services can sometimes be confused between advantages for a population and the building of empires[7]. The relationship between clinical volume and outcome is paramount for the design of clinical services that aim to improve the quality of care. It is an equally important issue for specialist training and the implementation of clinical trials.

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Short note

Expandable metallic stents for palliation of malignant pyloric and duodenal obstruction

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Introduction

Vomiting as a result of malignant obstruction of the pylorus or duodenum is a distressing symptom. Few patients are fit for operation and the outcome of other palliative measures is often unsatisfactory. Palliation of obstructing gastric carcinoma by means of self-expanding metallic stents was first described in 1992[1] but is perceived as technically challenging and has not been adopted widely.

Patients and methods

Between April 1999 and August 2000, 13 patients (eight men and five women of mean age 69·6 (range 49–87) years) underwent stent insertion (*Table 1*). All were assessed and turned down for surgical bypass. One patient with ampullary carcinoma had previously undergone biliary stenting.

Procedures were performed jointly by an experienced endoscopist and an interventional radiologist. Patients received supplemental oxygen and intravenous midazolam and pethidine.

Table 1 Underlying diagnoses and stent procedures

Diagnosis	No. of patients	Site of stent
Gastric carcinoma	6	Pylorus (6)
Recurrent oesophageal carcinoma	2	Pylorus (2)
Recurrent oesophageal carcinoma	1	Efferent loop, Roux-en-Y (1)
Ampullary carcinoma	2	Second part of duodenum (2)
Pancreatic carcinoma	1	Second part of duodenum (1)
Non-Hodgkin's lymphoma	1	Third part of duodenum (2)

Values in parentheses are the numbers of stents deployed

The stomach was intubated using a therapeutic duodenoscope (Olympus TJF-200®, Keymed, Southend, UK) and the proximal and distal margins of the stricture were defined by endoscopic injection of water-soluble contrast (Gastromiro®; Bracco, Milan, Italy) or by contrast study via an endoscopic catheter. A 0·089-cm hydrophilic guidewire – either Amplatz Superstiff® (AGA Medical, Golden Valley, Minnesota, USA) or Flexfinder® (Microvena, White Bear Lake, Minnesota, USA) – was passed down the working channel of the duodenoscope and across the stricture under direct vision and fluoroscopic screening.

A Wallstent Enteral® (Boston Scientific Microvasive, Natick, Massachusetts, USA) stent, 100 or 90 mm long (22 or 20 mm in final diameter), lubricated with silicon oil, was passed across the stricture over the guidewire. Eleven stents were delivered through the endoscope and three under fluoroscopic control after endoscope withdrawal. A duodenoscope with an elevating bridge was used to assist stent deployment across angulated strictures. Injection of contrast through the stent confirmed patency. Patients were allowed oral fluids as soon as they were awake.

Results

Stent placement (*Fig. 1*) was technically successful in all patients. Stenting abolished vomiting, allowing normal oral intake in ten patients. The median hospital stay was 6 days and median survival was 81 days. Six patients required no further inpatient care. Patients spent a median of 84 per cent of the duration of their terminal illness at home. Two patients' stents occluded within days of placement: one

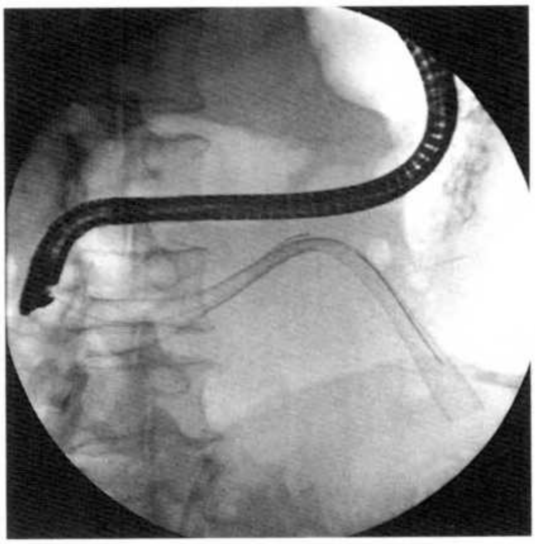

Fig. 1 Endoscopic–fluoroscopic placement of two overlapping enteral stents within the third part of the duodenum

required balloon dilatation and the other patient opted to have nasoenteral feeding. A third patient experienced occlusion after 3 months, which required dilatation and the insertion of an overlapping covered Ultraflex® (Boston Scientific Microvasive) stent. Four patients were admitted for terminal care unrelated to stent malfunction.

Discussion

The variation in duration of hospital stay and overall survival reflects a heterogeneous patient group at different stages of terminal illness, and variation in the time taken to arrange appropriate home care because of different levels of support available. As described for oesophageal stenting[2], occlusion was due to a non-malignant, hyperplastic, mucosal reaction and not to primary stent failure or malignant disease progression. The routine use of covered stents may minimize this reaction.

Uncovered Wallstent® enteral stents effectively palliate malignant pyloroduodenal obstruction in patients unfit for operation. The combined endoscopic–fluoroscopic approach is straightforward and well tolerated. Patients can be discharged promptly and cared for at home during the final illness. The procedure requires patience and a skilled team of nurses, endoscopist and radiologist working together.

The role of endoscopic stenting for malignant pyloroduodenal obstruction remains unclear. A randomized trial of stenting *versus* surgery would be difficult to perform. There is a need for prospectively collected observational data on both stenting and surgery, especially with regard to outcomes, quality of life and cost.

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Original article

Ultrasonography is superior to plain radiography in the diagnosis of pneumoperitoneum

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Background: The aim of this study was to compare plain radiography with abdominal ultrasonography in the detection of pneumoperitoneum.

Methods: A total of 188 patients with suspected hollow organ perforation were studied. All patients had abdominal ultrasonography, upright chest radiography and left lateral decubitus abdominal radiography examinations. The sensitivity, specificity, positive and negative predictive value, and accuracy of chest and abdominal radiography were compared with that of abdominal ultrasonography.

Results: One hundred and seventy-eight patients underwent laparotomy; 170 patients had hollow organ perforation, five patients had perforated appendicitis and three had acute cholecystitis. In the diagnosis of pneumoperitoneum, ultrasonography had improved sensitivity (92 *versus* 78 per cent), negative predictive value (39 *versus* 20 per cent) and accuracy (88 *versus* 76 per cent), and similar specificity (both 53 per cent) and positive predictive value (95 *versus* 94 per cent) compared with plain radiography.

Conclusion: Ultrasonography is more sensitive than plain radiography in the diagnosis of pneumoperitoneum.

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Introduction

Pneumoperitoneum results most commonly from a perforated hollow viscus. Plain radiography of the chest using a horizontal X-ray beam is a standard method for the detection of pneumoperitoneum[1,2]. Pneumoperitoneum can be demonstrated by plain radiography in 55–85 per cent of patients with hollow organ perforation[3,4]. Unfortunately, diagnosis based on upright chest radiography has practical limitations. Many patients with an acute abdomen or acute trauma are too sick or debilitated to stand up for erect chest radiographic examinations[5,6]. Alternatively, a left lateral decubitus radiograph of the abdomen can also demonstrate pneumoperitoneum. However, plain radiography has the inherent disadvantage that the presence and extent of abnormal lucency may not accurately reveal the extent of pneumoperitoneum. Although computed tomography (CT) is superior to erect chest radiography in demonstrating free intraperitoneal air, it is neither practical nor cost effective in patients with an acute abdomen[7].

Ultrasonography has emerged as an alternative initial diagnostic procedure in patients with an acute abdomen[8–13]. Although several reports have documented the detection of free intraperitoneal air in patients with acute abdominal disorders, the relative sensitivity and specificity of ultrasonography remains unclear[14–16]. The aim of this study was to compare ultrasonography with plain radiography in the detection of pneumoperitoneum.

Patients and methods

Between March 1996 and September 2000, 188 patients with suspected hollow organ perforation admitted to the Department of Emergency Medicine, National Taiwan University Hospital, were enrolled in the study. There were 140 men and 48 women, with a mean age of 51 (range 15–88) years. After a detailed history and a complete physical examination, erect chest radiography was performed in each patient in the radiology department. A left lateral decubitus abdominal film was taken if the chest radiograph failed to reveal free intraperitoneal air. Pneumoperitoneum was diagnosed by staff radiologists. After complete radiographic examination, the patient was brought back to the emergency department for ultrasonographic examination by a blinded ultrasonographer (staff surgeon or staff emergency physician). Intramuscular analgesia (meperidine hydrochloride 50 mg) was given to patients in pain before ultrasonography.

Because free air rises to the highest accessible portion of the peritoneal cavity, it usually overlies the liver anteriorly. Abdominal ultrasonography was first performed over the epigastric area (supine position) followed by the highest point of the right hypochondrium (left lateral position) using a hand-held 3·75-MHz curved array transducer (Toshiba SSA-340A; Toshiba, Tochigi-Ken, Japan). The results of the ultrasonographic examination were classified as either positive or normal. A positive ultrasonographic finding included any additional or abnormal changes in the abdominal cavity, including pneumoperitoneum.

Ultrasonographic evidence of pneumoperitoneum was sought as echogenic lines or spots with posterior ring-down or comet-tail reverberatory artefacts between the anterior surface of the left lobe of the liver and the anterior abdominal wall on the epigastric scan, and between the right lobe of the liver and the inner thoracic wall on the right hypochondrial scan[14].

The decision to operate was based on the presence of pneumoperitoneum on either ultrasonography or plain radiography, or the presence of peritonitis on clinical examination. Patients without free air were observed in hospital and investigated as necessary. Additional panendoscopy or CT was performed to search for the diagnosis. Operative findings were related to ultrasonographic findings to determine the diagnostic accuracy of ultrasonography. The sensitivity, specificity, positive and negative predictive value, and accuracy of ultrasonography were calculated and compared with those obtained for plain radiography in the diagnosis of pneumoperitoneum.

Results

Ultrasonography was performed in all 188 patients. The ultrasonographic findings are shown in *Table 1*. There were 165 patients with the ultrasonographic finding of free air; 23 patients had no free air. Among the 178 patients who had surgery, 165 patients were thought to have hollow organ perforation and 13 to have peritonitis. A total of 170 proved to have hollow organ perforation at laparotomy (*Table 2*).

Table 1 Findings of abdominal ultrasonography in 188 patients with acute abdominal pain

	No. of patients
Abnormal scan result	178
Pneumoperitoneum	165
Fluid accumulation	
Subhepatic area	151
Pelvis	83
Small bowel dilatation	120
Thickness of antrum or duodenal wall	67
Normal scan result	10

Panendoscopy on seven patients who did not have a laparotomy revealed peptic ulceration without perforation in all. These patients received an H_2 blocker and antacid treatment. A further three patients who did not have laparotomy underwent abdominal CT which showed no abnormality; they received conservative treatment and were discharged 2–3 days later, once the abdominal pain had ceased. The symptoms in all ten patients with normal imaging resolved without operation, and full recovery was verified in outpatients 2 weeks later.

Of the 165 patients with free air found by ultrasonography, hollow organ perforation was confirmed in 157 during operation. The ultrasonographic diagnosis of pneumoperitoneum was incorrect in eight patients, including five who had perforated appendicitis and three with acute cholecystitis.

Free air was detected by upright chest radiography in 126 patients, and 120 of these were found to have hollow organ perforation at operation. A further 62 patients underwent additional left lateral decubitus abdominal radiography; 16 were diagnosed with pneumoperitoneum but only 14 patients were found to have hollow organ perforation.

In the diagnosis of pneumoperitoneum, ultrasonography had a sensitivity of 92 per cent, a specificity of 53 per cent, a positive predictive value of 95 per cent, a negative predictive value of 39 per cent and an accuracy of 88 per cent. Plain radiography had a sensitivity of 78 per cent, a specificity of 53 per cent, a positive predictive value of 94 per cent, a negative predictive value of 20 per cent and an accuracy of 76 per cent.

Discussion

Hollow organ perforation is one of the most common surgical emergencies. The diagnosis of hollow organ perforation is usually based on the presence of free intraperitoneal air on chest or abdominal radiography. Free air is missed on upright posteroanterior chest radiographs in 20–62 per cent[7,16]. Adding a left lateral decubitus

Table 2 Intraoperative findings in 178 patients who underwent laparotomy for acute abdominal pain

	No. of patients
Perforated duodenal ulcer	77
Perforated gastric ulcer	58
Colonic perforation	26
Intestinal perforation	9
Perforated appendicitis	5
Acute cholecystitis	3

film improves the sensitivity of the examination: in the present study it revealed free intraperitoneal air in 14 patients. Woodring and Heiser[7] found that erect lateral chest radiography was a more sensitive detector of free air than upright posteroanterior chest radiography.

It is well known that CT is the most sensitive imaging test for the detection of free intraperitoneal air[16–19]: the success rate is between 83 and 100 per cent[16,17,20,21]. However, CT is expensive and generates more radiation than plain radiography. Ultrasonography can detect 76–90 per cent of patients with pneumoperitoneum, but all previous studies included only a limited number of patients[22–24]. The present study included a larger number of patients and demonstrated that ultrasonography is a useful alternative imaging modality for the detection of pneumoperitoneum.

The amount of free air produced after perforation of the lower gastrointestinal tract was usually large and both plain radiography and ultrasonography had similar accuracy in detecting pneumoperitoneum (100 per cent for both in 26 colonic perforations). The amount of free air from the upper gastrointestinal tract was usually lower, and this study found that ultrasonography was superior to plain radiography in this setting. The ability of ultrasonography to detect gas is due to total sound reflection, which is the result of reverberation between the gas and the transducer[25,26].

There are some pitfalls to be avoided during ultrasonographic imaging for pneumoperitoneum, including overlying rib reflection, ring-down artefacts from adjacent air-filled lung, and interposition of the colonic gas anterior to the liver[27]. In the present study, eight false-positive ultrasonographic examinations resulted from the finding of abnormal images on either the right hypochondrial or the epigastric scan. To prevent the echo pattern visible in the pleurodiaphragmatic recess from being misinterpreted as free air, modification of the patient's position from supine to left lateral during the examination is essential because it permits confirmation of the origin of the interference echo pattern.

Ultrasonography has the additional advantage of detecting other findings associated with pneumoperitoneum that were not found on the plain radiographs. It is, however, operator dependent[12]; for an independent ultrasonographer to perform ultrasonography and interpret the results with accuracy, adequate training is required. Radiologists are not available for 24 h of the day; therefore it is inevitable that ultrasonography is performed by other trained physicians[28,29].

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Original article

Treatment and outcome of pancreatic venous graft thrombosis after kidney–pancreas transplantation

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Background: Pancreas venous graft thrombosis after transplantation is the main non-immunological cause of graft failure and usually results in pancreatectomy. Duplex Doppler ultrasonography is the primary imaging technique for monitoring vascular patency after pancreas transplantation. This study reports the results of rescue treatments for pancreas graft thrombosis after simultaneous pancreas–kidney transplantation.

Methods: One hundred and ninety-six patients with insulin-dependent diabetes mellitus received a simultaneous pancreas–kidney transplantation. Venous graft thrombosis was diagnosed in 25 of these patients based on Doppler ultrasonographic findings.

Results: Total venous graft thrombosis was diagnosed in 20 symptomatic patients, of whom 14 required graft pancreatectomy. Surgical thrombectomy was attempted in six patients with preserved arterial supply and was successful in four. Partial venous graft thrombosis was diagnosed in five asymptomatic patients; one also had partial splenic artery thrombosis. Rescue graft procedures included systemic anticoagulation (one patient), arterial thrombolysis (one) and venous thrombolysis and/or mechanical venous thrombectomy (four episodes in three patients). Graft rescue was achieved in three patients treated by venous thrombolysis/thrombectomy.

Conclusion: Doppler ultrasonography allows the appropriate selection of rescue treatment based on the findings of total or partial thrombosis.

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Introduction

In recent years, advances in various fields, such as organ preservation, surgical technique, immunosuppression and early detection and treatment of postoperative complications, have resulted in improved patient and graft survival after pancreas transplantation. According to the International Pancreas Transplant Registry, nearly 14 000 pancreas transplantations have been performed up until August 2000, with an overall 1-year graft survival rate of 84 per cent and patient survival rate of 94 per cent. However, the rate of technical failure after pancreas transplantation is higher than that for other solid organ transplants. The most common causes of technical failure are intra-abdominal infection, graft thrombosis and graft pancreatitis resulting in operative reintervention. In several reports there is a wide variation in the incidence of graft thrombosis ranging from 10 to 35 per cent[1–7]. Graft pancreatectomy remains the most common treatment after acute graft thrombosis, although in selected patients immediate pancreatic re-transplantation has been reported[8–10]. There are also reports in which partially or completely thrombosed allografts were salvaged with surgical thrombectomy or anticoagulation[6,8,11].

This report describes the diagnostic strategy for detecting early graft thrombosis in symptomatic and asymptomatic patients, and the outcome of alternatives for rescue treatment using surgery or interventional angiographic procedures. The benefits of salvage procedures are weighed against their morbidity.

Patients and methods

Some 196 patients underwent simultaneous kidney–pancreas transplantation between February 1986 and December 2000. There were 132 men and 64 women, with a mean(s.d.) age of 36(6) years and duration of insulin-dependent diabetes mellitus of 21(5) years.

Pancreas transplantation

The pancreas was preserved under cold storage conditions with University of Wisconsin solution in the majority of cases, with a mean(s.d.) cold ischaemia time of 5(2) (range 3–14) h. The pancreas graft was situated in the right iliac fossa. The pancreatic arterial reconstruction was performed with a donor iliac artery bifurcation graft anastomosed to the splenic and superior mesenteric arteries in 30 cases, while in 166 an end-to-end anastomosis was created between the distal portion of the superior mesenteric artery (SMA) and the opening of the splenic artery[12]. Arterial revascularization of the allograft was carried out either by anastomosing the proximal end of the SMA or the donor iliac artery to the iliac artery of the recipient. Venous anastomosis was performed between the portal vein of the graft and the vena cava (75 per cent) or iliac vein (25 per cent) of the recipient. No portal venous extension was carried out. The exocrine secretions were drained either into the bladder (n = 106) or to the small bowel (n = 90).

Postoperative immunosuppression consisted of prednisone and cyclosporin in the first four patients of this series. The following 113 patients were treated with quadruple therapy (cyclosporin, prednisone, azathioprine and either prophylactic antilymphoblast globulin or OKT3); in the last 79 patients azathioprine was replaced by mycophenolate mofetil, and in 26 patients cyclosporin was replaced by tacrolimus. Prophylactic anticoagulation with subcutaneous low molecular weight heparin (Fragmin®; Pharmacia and Upjohn; Barcelona, Spain) 2500 units per 12 h was given during the first 10 days; thereafter the patients received aspirin until discharged from hospital.

Postoperative monitoring

Postoperative monitoring included daily clinical examination and collection of laboratory data, including serum glucose, creatinine and pancreatic enzyme (serum/urine) levels, and full blood count. To assess arterial and venous flow throughout the pancreas graft, Doppler ultrasonography was performed with a Toshiba SSA 100 A (22 patients), SSH 140 A or Powervision (174 patients) scanner (Toshiba, Nasu, Japan), with colour capabilities, using a 3·75-MHz transducer. A baseline study was carried out at 24–72 h after grafting and weekly thereafter, or when clinically indicated (unexplained fever, abdominal pain over the pancreatic graft, decrease in urinary amylase levels of more than 50 per cent in patients with bladder drainage, hyperglycaemia, increase in serum amylase levels or raised white cell count). Pancreas size, echostructure and intra-abdominal fluid collections around the pancreas were evaluated by real-time ultrasonography. Pulsed Doppler and colour Doppler examination included the assessment of arterial and venous graft vessels from the iliac anastomosis, carefully followed along the graft to the distal portion of the mesenteric and splenic arteries and vein. The arterial and venous spectra were also obtained at the level of the parenchyma (head, body and tail). The arterial waveform was quantified by the resistive index. Doppler scales were adjusted to optimize the detection of low blood flow velocities.

Results

Twenty-five (13 per cent) of 196 simultaneous kidney–pancreas transplants developed pancreas venous graft thrombosis. There were 15 men and ten women with a mean(s.d.) age of 40(6) years. In 15 patients exocrine secretions were drained into the bladder while in ten they were diverted to the small bowel. The mean(s.d.) cold ischaemic time was 6·7(2·4) (range 3–12) h. Graft thrombosis was diagnosed a mean(s.d.) of 4·2(2·1) (range 1–10) days after transplantation.

Patients with pancreas venous thrombosis were analysed in two groups (total and partial venous graft thrombosis) according to the Doppler ultrasonographic findings at diagnosis.

Total vein thrombosis

Twenty patients (10 per cent) developed total venous graft thrombosis. The diagnosis was made by Doppler ultrasonography when no venous flow was visualized, combined with an increased arterial resistance obtained at hilar and parenchymal levels[13,14]. All patients in this group were symptomatic: 11 (56 per cent) had hyperglycaemia, 8 (36 per cent) had abdominal pain over the pancreas graft, 5 (25 per cent) had hyperamylasaemia, and 4 (20 per cent) had a combination of an increase in serum glucose levels and pain over the graft. Graft thrombosis, determined by the time of sonographic diagnosis, occurred a mean of 4·4 (range 1–9) days after transplantation.

In 14 patients immediate relaparotomy confirmed complete pancreatic graft necrosis; pancreatectomy was required in 13, all of whom had an uneventful postoperative course. On histological examination there was venous thrombosis without arterial thrombosis in all the grafts. In the final patient transplant pancreatectomy was followed by successful immediate pancreatic retransplantation.

In five patients laparotomy revealed a partial graft necrosis with a well preserved arterial supply, and surgical thrombectomy was attempted. The ligatures at the distal ends of both the splenic and mesenteric veins were identified and released for the introduction of a Fogarty catheter until the portacaval or portoiliac anastomosis was reached. The balloon catheter was inflated and the thrombotic material carefully removed. These manoeuvres were repeated until backbleeding was established, after which both venous openings were again tied off. The pancreas graft changed colour and decreased in size in all five patients. In the remaining patient the pancreatic tail was twisted, suggesting a mechanical cause for the splenic vein thrombosis. In this patient a pancreatic tail resection was performed together with surgical thrombectomy.

All patients were anticoagulated with heparin for 3–6 months. Follow-up of the rescued grafts included Doppler ultrasonography 24 h after the procedure and twice in the first week; thereafter the standard protocol was followed. The rescue treatment was unsuccessful in two patients resulting in pancreatectomy within 36 h of reoperation, followed by an uneventful recovery. In the remaining four patients graft salvage was successful, achieving good pancreatic function and immediate recovery of Doppler variables. Two patients developed complications: one had a leak at the duodenovesical anastomosis with a vesicocutaneous fistula, necessitating reoperation 6 weeks later. The other patient underwent reoperation 78 h after graft salvage for bleeding, although no single bleeding vessel was identified at laparotomy. All four patients with a successfully salvaged transplant had good pancreatic and kidney function; they remained insulin-free for 50, 48, 44 and 38 months. One of these normoglycaemic patients died 48 months after graft rescue from a myocardial infarct.

Partial vein thrombosis

There were five asymptomatic, normoglycaemic patients (3 per cent) in whom routine Doppler ultrasonography suggested the diagnosis of partial thrombosis (mesenteric vein, one; splenic vein, four) at 6·8 (range 5–10) days after transplantation. The diagnosis was established when a thrombus was seen filling the vein lumen without complete occlusion on real-time ultrasonography, in addition to maintained venous flow peripheral to the thrombus (*Fig. 1*), and into the graft parenchyma. A low-resistance arterial Doppler flow (resistive index less than 0·75) was also obtained at hilar and parenchymal levels.

One patient with partial thrombosis at the distal end of the splenic vein was treated with heparin. The anticoagulation was withdrawn 3 days later because of an extensive perirenal haematoma. The splenic vein thrombosis progressed on Doppler ultrasonography; surgical intervention was therefore indicated to attempt venous thrombectomy. Rescue treatment was not feasible since the graft had extensive areas of parenchyma necrosis, and a pancreatectomy was performed.

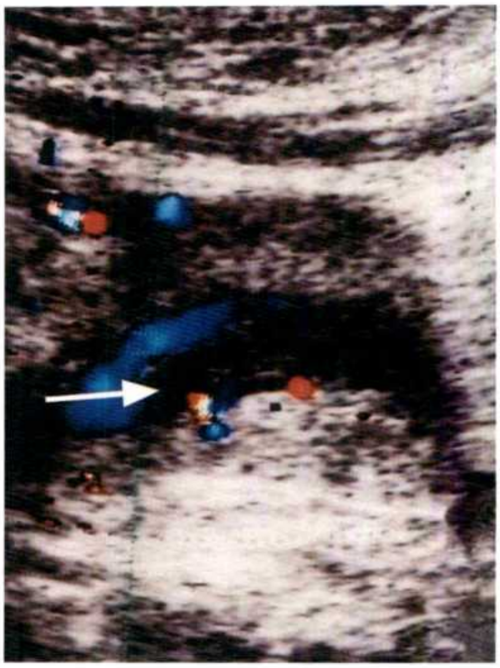
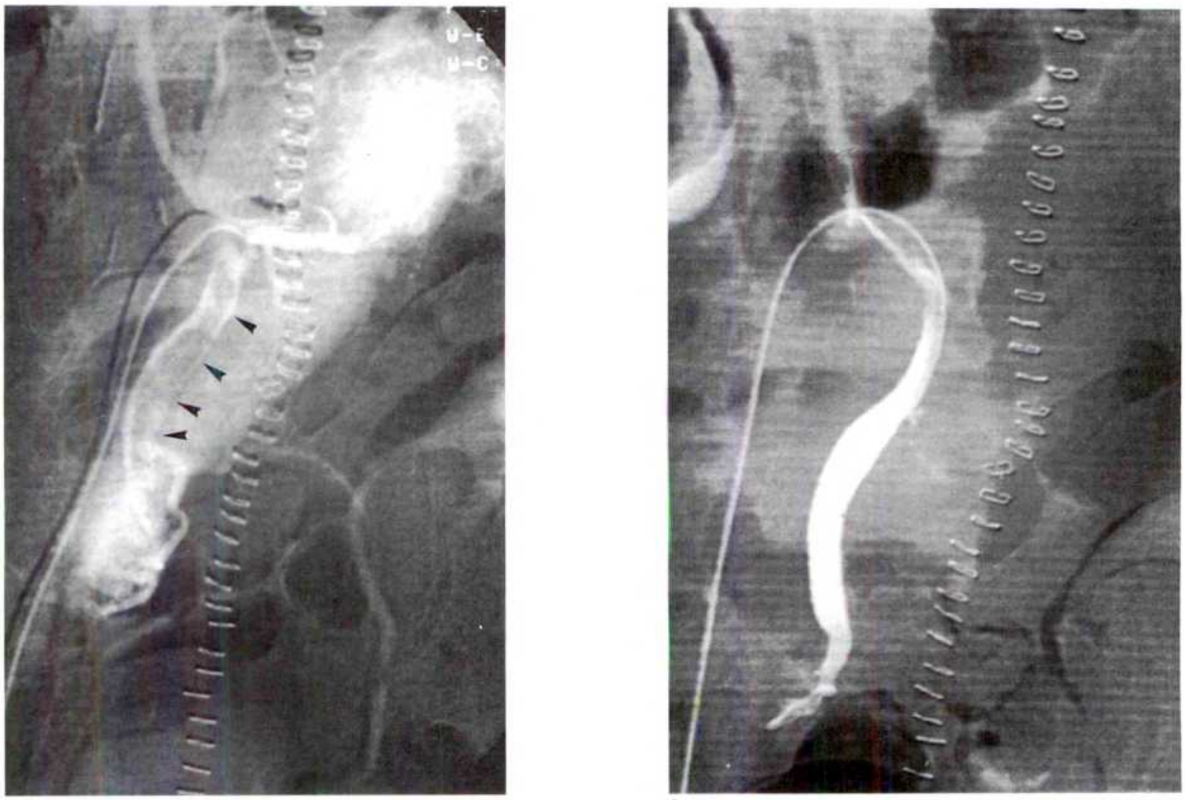


Fig. 1 Colour Doppler ultrasonography of the splenic vein, showing a hypoechoic thrombus (arrow) partially filling the lumen, with maintained peripheral (colour Doppler) venous flow

The other four patients were treated with percutaneous interventional vascular procedures (catheter-directed thrombolysis and/or mechanical thrombectomy). In these patients selective pancreas graft arteriography was performed to confirm the diagnosis and to determine the precise location and extent of the partial thrombosis. The time that elapsed between the Doppler ultrasonographic diagnosis and the angiographic study was 2 h in two patients, and 24 h in the remaining two patients. Arteriography confirmed the diagnosis of partial venous thrombosis in all patients, but in one also disclosed a partial thrombosis in the distal portion of the splenic artery. In this patient catheter-directed thrombolysis was done through the splenic artery (two boluses of 400 000 and 300 000 units urokinase, each over 20 min and 20 min apart). In the remaining three patients a right femoral vein puncture was performed and a catheter was advanced through the portal vein into the splenic or mesenteric vein. A urokinase infusion (300 000 units over 20 min) was carried out in one patient with partial mesenteric vein thrombosis. Percutaneous mechanical thrombectomy with an Angiojet® catheter (Possis Medical, Minneapolis, Minnesota, USA) was carried out in the remaining two. In



a Before thrombectomy

b After thrombectomy

Fig. 2 a Venous phase of selective arteriography demonstrates the extensive partial thrombus (arrowheads) at the splenic vein. b Selective venography after percutaneous mechanical thrombectomy confirms complete removal of the thrombus

one of the latter thrombectomy was followed by adjunctive therapy with urokinase (300 000 units over 20 min) (*Fig. 2*).

Percutaneous mechanical thrombectomy and/or urokinase infusion achieved technical success, with patency restored on selective venographic study carried out after the procedure, in all three patients with isolated partial venous thrombosis. Thrombolysis failed in the patient with combined arterial and venous thrombosis who required transplant pancreatectomy. Patients who had successful rescue treatment followed the same anticoagulation and follow-up protocol as those who underwent surgical thrombectomy. Complications were observed in two. The patient treated only with a urokinase venous infusion developed a fever shortly after the procedure, and the chest radiograph showed radiological features consistent with pulmonary embolism that was confirmed by a ventilation–perfusion scan. The same patient also had an episode of mild gastrointestinal haemorrhage such that the anticoagulation was reduced. The other patient developed a haematoma surrounding the kidney graft 6 days after mechanical thrombectomy and required withdrawal of the anticoagulation. Thirty days later a recurrence of the partial thrombus was diagnosed by Doppler ultrasonography performed during the follow-up of a biopsy-proven kidney graft rejection episode. Meanwhile the patient remained normoglycaemic and asymptomatic. Mechanical thrombectomy was repeated, followed by adjunctive therapy with urokinase infusion (500 000 units over 20 min), once again achieving lysis of the thrombus, without postprocedural complications. Currently the three successfully treated patients have good pancreatic and kidney function, and remain insulin-free after 46, 38 and 34 months.

Discussion

Although graft rejection remains the leading cause of both short- and long-term pancreas transplant failure, vascular complications are the second most common cause and contribute significantly to graft loss, as well as morbidity and death[1,6]. In contrast to other solid organs transplanted, the pancreas is susceptible to vascular thrombosis because of the intrinsic low microcirculatory flow in the parenchyma. Other predisposing factors include long preservation time, left-sided graft placement resulting in deeper anastomosis and the use of a venous extension. Recently Ciancio *et al.*[15] pointed out that intravenous use of tacrolimus induction therapy might be a possible risk factor in the development of venous graft thrombosis. In the present study a few patients received oral tacrolimus but none had venous graft thrombosis.

Because of the late diagnosis and the lack of safe procedures for pancreatic graft rescue, thrombosis of a pancreatic graft usually leads to transplant pancreatectomy[16–18]. Occasionally the availability of a suitable donor allows immediate retransplantation. There are isolated reports of pancreatic graft salvage after venous or simultaneous arterial and venous graft thrombosis[6,8,19–22]. Portal venous thrombectomy was reported by Douzdjian *et al.*[23] in two patients, but both presented with graft pancreatitis. Acute respiratory distress syndrome developed in one patient who needed graft pancreatectomy and another patient died after the operation. These authors concluded that surgical thrombectomy was dangerous because of the life-threatening complications. This contrasts with results in the present study, in which management was based on an early diagnosis by Doppler ultrasonography and prompt surgical thrombectomy. In the patients with total thrombosis but normal arterial flow, thrombectomy achieved graft rescue in four patients with long-term patient and graft survival. Similar results of surgical venous thrombectomy have been reported recently by Ciancio *et al.*[24] in three patients.

The use of advanced ultrasound technology (colour and power Doppler) allowed the diagnosis of partial vein thrombosis in five asymptomatic patients. Systemic anticoagulation was given to two patients (in one after failed arterial thrombolysis), but did not prevent the progression of vascular thrombosis. However, percutaneous interventional procedures were successful in three patients with isolated partial venous thrombosis. Selective catheter thrombolysis at the mesenteric vein achieved the complete restoration of venous outflow in one. This patient suffered pulmonary thromboembolism due to thrombus dislodgement, a known complication of fibrinolytic treatment. Percutaneous mechanical thrombectomy was undertaken in the next two patients diagnosed with partial venous graft thrombosis at the splenic vein. This technique is an alternative to thrombolysis, and has been used in renal graft vein thrombosis[25]. In this unit the procedure was performed with an Angiojet catheter. This is a double-lumen catheter with an outer diameter of 5 Fr, which fragments and removes thrombus by means of high-pressure saline jets, reducing the risk of thromboembolism.

Careful clinical monitoring after interventional angiographic procedures is essential because of the risks associated with anticoagulation. These clinical results emphasize the importance of prompt diagnosis, and an integrated radiological and surgical management that obtained rates of graft rescue as high as 67 per cent after surgical thrombectomy and 75 per cent after percutaneous interventional vascular procedures in suitable patients.

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Original article

Postoperative enterococcal infection after treatment of complicated intra-abdominal sepsis

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Background: The prevalence of enterococcal isolation and factors associated with postoperative enterococcal infection remain ill defined.

Methods: A prospective longitudinal observational study was conducted of consecutive patients with a first episode of intra-abdominal infection and a positive microbiological culture who did or did not develop a postoperative septic complication involving enterococci. The prevalence of initial enterococcal isolation was determined for each focus of infection. Postoperative enterococcal infections were related to whether appropriate (piperacillin–tazobactam), suboptimal (carbapenems) or inappropriate (cefotaxime plus metronidazole) antienterococcal therapy had been administered empirically.

Results: Enterococci were isolated in 42 (21 per cent) of the 200 patients investigated. The isolation rates were 11 per cent for community-acquired peritonitis, 50 per cent for postoperative peritonitis and 23 per cent for intra-abdominal abscesses of both origins. No enterococci were isolated from 49 patients with perforated appendicitis. Independent factors for postoperative enterococcal infection were type of intra-abdominal infection ($P = 0.006$), Acute Physiology And Chronic Health Evaluation (APACHE) II score greater than 12 ($P = 0.04$) and inappropriate empirical antibiotic cover ($P = 0.05$). Postoperative enterococcal infections were associated with a high mortality rate (21 *versus* 4 per cent; $P < 0.0007$).

Conclusion: Enterococci are frequently isolated from intra-abdominal infections of non-appendiceal origin and are often involved in postoperative infectious complications, particularly peritonitis. Empirical antibiotic therapy covering *Enterococcus faecalis* should be contemplated in some circumstances.

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Introduction

Over the past two decades the enterococci have become important nosocomial pathogens and currently there are concerns about the development of resistance by enterococci to many antibiotics and their involvement in failure of treatment of established intra-abdominal infection[1]. Although more than ten different species of enterococci have been described, almost 100 per cent of all clinical isolates are represented by *Enterococcus faecalis* (80–90 per cent of isolates) and *E. faecium*[2]. The enterococci are commensals of the gastrointestinal tract and have well typified virulence factors that allow them to bind to epithelial and serosal surfaces and to elicit an immune and inflammatory response[3].

Some of the well established antibiotic regimens for the treatment of intra-abdominal infection are based on combinations of cephalosporins or aminoglycosides plus an antianaerobic agent not covering the enterococci. Monotherapy with carbapenems is suboptimal for these micro-organisms[4]. Only triple therapy including a β-lactam agent or monotherapy with piperacillin–tazobactam would afford optimal coverage against enterococci. There is, however, an ongoing controversy[5,6] around the potential superiority of antibiotic regimens that cover the enterococci. This may be due in part to inappropriate patient stratification according to whether or not enterococci are isolated from the primary septic focus.

This investigation aimed to define the prevalence and associated clinical and bacterial variables for enterococcal isolation in diffuse or localized peritonitis, and factors associated with postoperative enterococcal infection.

Patients and methods

Over a 5-year period (1994–1999) patients with an initial episode of intra-abdominal abscess or diffuse peritonitis were investigated prospectively for the presence of *Enterococcus* species and the development of postoperative septic complications. Patients with community-acquired or nosocomial intra-abdominal infection due to hollow viscus perforation or anastomotic dehiscence (postoperative peritonitis after an elective procedure) were included if: (1) bacteriological culture of the intra-abdominal exudate was positive; (2) an intra-abdominal abscess was identified at laparotomy or computed tomography, or diffuse peritonitis was confirmed at operation; (3) they were not receiving antibiotics at the time intra-abdominal infection was diagnosed; (4) they were treated by surgery or percutaneous drainage and received one of the following well established[7,8] antibiotic regimens – cefotaxime (1 g per 6 h) plus metronidazole (0·5 g per 8 h), carbapenems (imipenem 0·5 g per 6 h or meropenem 1 g per 8 h) or piperacillin–tazobactam (4 g per 8 h); and (5) postoperative follow-up of at least 30 days was obtained.

Exclusion criteria were previous antibiotic treatment (excluding a single dose of prophylactic antibiotics), pregnancy, an Acute Physiology And Chronic Health Evaluation (APACHE) II score greater than 30, peritonitis after abdominal trauma, pancreatic infection, non-perforated appendicitis or cholecystitis, and treatment with steroids or immunosuppressive drugs.

Microbiological samples were processed by standard microbiological techniques including culture on agar plates enriched with colistin and nalidixic acid (CNA medium) to isolate selectively the streptococci and *Enterococcus* spp.[2].

Patients were observed until death or discharge for the development of the following postoperative septic complications: (1) wound infection[9]; (2) intra-abdominal abscess or peritonitis, defined as radiological or direct (at relaparotomy) proof of recurrence or persistence of intra-abdominal infection; and (3) distant infection, defined as pneumonia (fever plus radiological proof), catheter-related bacteraemia (blood and catheter-tip culture positive for the same micro-organism) or urinary infection (leucocyturia plus positive urine culture).

The prevalence of enterococcal isolation was investigated for each of the following five septic foci: biliary, gastroduodenal, small bowel, appendiceal and colonic.

Patients with or without enterococci isolated from the initial microbiological sample were compared with respect to age and sex, severity of underlying disease using the APACHE II[10] and Elebute[11] scores, focus of sepsis, co-isolated micro-organisms, response to empirical antibiotic therapy, and prevalence of enterococcal reinfection or superinfection. Enterococcal reinfection was defined as the isolation of enterococcus from a septic postoperative complication in patients in whom enterococcus had previously been isolated from the initial sample. Enterococcal superinfection was defined as the isolation of the pathogen from a postoperative septic complication in patients in whom enterococci were not present in the initial microbiological sample.

The χ^2 test was used to compare prevalence rates and the two-tailed Student's t test for unpaired samples to compare means of quantitative variables normally distributed. Statistical significance was set at $P < 0{\cdot}05$. Logistic regression analysis was carried out to investigate the relative contribution of different factors to the development of a postoperative enterococcal infection.

Results

Two hundred patients (126 males, 74 females) with a mean(s.d.) age of 59(19) (range 8–93) years were investigated. Enterococci were isolated in 42 (21 per cent) of the patients. Thirty-five (83 per cent) of the isolates were *E. faecalis* and seven (17 per cent) *E. faecium*. Only one patient had a monomicrobial enterococcal secondary peritonitis, after a gastric perforation, due to *E. faecium*; the remaining 41 patients had polymicrobial infections. In two of the 42 patients (5 per cent) enterococci were also recovered from the blood cultures. Enterococcal isolation rates were 11 per cent for community-acquired peritonitis (n = 113), 50 per cent for postoperative peritonitis (n = 34) and 23 per cent for intra-abdominal abscesses of either origin (n = 53). No enterococci were isolated from 49 episodes (seven abscesses, 42 diffuse peritonitis) of perforated appendicitis. For non-appendiceal sites, the prevalence of enterococcal isolation was 23 of 67 (34 per cent) for colon, 7 of 33 (21 per cent) for liver and bile tract, 6 of 27 (22 per cent) for gastroduodenal and 6 of 22 (27 per cent) for the small bowel.

The presence of enterococci in the initial sample was associated with older age, more severe disease, co-isolation of *Pseudomonas* spp., higher number of concurrent bacterial species isolated from the same sample and a higher rate of postoperative enterococcal infection (*Table 1*).

Postoperative septic complications with participation of enterococci were observed in 34 patients (17 per cent); 30 were due to *E. faecalis* and four to *E. faecium*. In 15 they represented a reinfection and in 19 a superinfection. Diagnosis was 20 wound, six intra-abdominal and eight distant infections. Of these, nine were monomicrobial and all were due to *E. faecalis*. The clinical and bacteriological

Table 1 Clinical and bacteriological differences between patients with a first episode of intra-abdominal infection involving *Enterococcus* and without an enterococcal infection

	With *Enterococcus* (n = 42)	Without *Enterococcus* (n = 158)	P¶
Age (years)*	67·8(14)	57·4(20)	0·002
Sex ratio (M : F)	24 : 18	103 : 55	n.s.
APACHE II score*	10·3(4)	8·1(1)	0·002
Elebute score*	10·6(4)	8·9(4)	0·04
Septic complications†	27 (64)	68 (43)	0·01
Wound infection†	12 (29)	44 (28)	n.s.
Intra-abdominal abscess†	6 (14)	9 (6)	0·06
Other†‡	10 (24)	16 (10)	0·02
Streptococcus spp.†§	16 (39)	17 (11)	< 0·001
Pseudomonas aeruginosa†§	10 (23)	11 (7)	0·002
Candida spp.†§	2 (5)	17 (11)	n.s.
Mean no. of different species	3·1	2·2	< 0·001
Enterococcal reinfection†	15 (36)	—	
Enterococcal superinfection†	—	19 (12)	
Mortality†	3 (7)	9 (6)	n.s.

*Values are mean(s.d.). †Values in parentheses are percentages. ‡Urinary, pneumonia or catheter-related bacteraemia. §Rate of isolation of bacteria other than *Enterococcus* from the same initial sample. APACHE, Acute Physiology And Chronic Health Evaluation; n.s., not significant. ¶Student's t and χ^2 tests

Table 2 Baseline clinical and bacteriological differences between patients with or without a postoperative enterococcal infection

	Postoperative enterococcal infection		
	Present (n = 34)	Absent (n = 166)	P§
Age (years)*	70·1(12)	57·4(20)	< 0·001
APACHE II score*	11·8(4)	7·9(5)	< 0·001
Elebute score*	11·3(4)	8·9(4)	0·006
Primary infection†			< 0·001
Abscess	9 (27)	45 (27)	
Secondary peritonitis	11 (32)	101 (61)	
Postoperative peritonitis	14 (41)	20 (12)	
Pseudomonas aeruginosa†‡	9 (26)	12 (7)	< 0·001
Mean no. of different species‡	3·0	2·3	< 0·001
Mortality†	7 (21)	7 (4)	< 0·001
Cefotaxime + metronidazole (n = 123)†	22 (18)	101 (82)	
Carbapenems (n = 41)†	11 (27)	30 (73)	
Piperacillin–tazobactam (n = 36)†	1 (3)	35 (97)	0·02

*Values are mean(s.d.). †Values in parentheses are percentages. ‡Isolated from the same initial sample. APACHE, Acute Physiology And Chronic Health Evaluation. §Students t and χ^2 tests

profiles of patients presenting a postoperative enterococcal infection are shown in *Table 2*. They were older, had worse disease severity scores and a fivefold higher mortality rate than those without a postoperative enterococcal infection. *Table 3* shows the more relevant independent factors for postoperative enterococcal infection.

To investigate further the relationship of postoperative enterococcal infection with inappropriate antibiotic therapy, a separate analysis was carried out for the subgroup of 123 patients receiving cefotaxime plus metronidazole. In these patients, age, severity of disease, type of infection, source of sepsis and presence of enterococcus in the initial sample were factors associated with the development of postoperative enterococcal infection (*Table 4*).

Patients with enterococcal superinfection were analysed, excluding the less severe cases of perforated appendicitis (*Table 5*). Age and severity of disease were again factors related to postoperative enterococcal infection, and this translated into a higher mortality rate. Furthermore, co-isolation of *Pseudomonas* spp. and absence of fungi in the initial sample were distinctive features of patients developing an enterococcal superinfection.

Fourteen patients (7 per cent) died after operation, 12 of them due to an infectious complication. Differences between survivors and non-survivors are shown in *Table 6*. Patients who died differed in age, severity of the infection and the prevalence of *E. faecalis* isolation from a postoperative septic complication.

Discussion

In the present series *Enterococcus* was isolated from one-fifth of patients, an almost identical prevalence to that reported by Barie *et al.*[4] and Burnett *et al.*[12] in two series with a very similar mix of patients. In the present study the participation of enterococci in intra-abdominal infections was determined largely by the anatomical site of infective origin[12]. No patient with perforated appendicitis had enterococci isolated from the peritoneal cavity. A low enterococcal isolation rate in complicated appendicitis of 9 per cent was also reported by Burnett *et al.*[12]. This is, however, at variance with the findings of Hopkins *et al.*[13] who reported isolation of enterococci in 21 (18 per cent) of 114 patients with gangrenous or perforated appendicitis. Because age is a relevant factor influencing the participation of *Enterococcus* in intra-abdominal sepsis[12], it may be speculated that this micro-organism infrequently colonizes the gastrointestinal tract of young patients with appendicitis. In addition all subsets of patients in whom enterococci were initially isolated also had a higher number of other species co-isolated per sample. This suggests that the ecological basis for enterococcal infection may involve a more heavily colonized gastrointestinal tract, often including *Pseudomonas aeruginosa*; both may be a feature of advanced age.

Current recommendations for empirical antibiotic therapy of intra-abdominal infections do not put major emphasis on covering the enterococci[14,15]. With few exceptions[16–18], most of the studies recently published on the subject do not include β-lactam agents, the most

Table 3 Multiple regression analysis of risk factors for postoperative enterococcal infection

Risk factor	Odds ratio
Postoperative peritonitis	4·4 (0·9, 22·6)
APACHE II score > 12	3·4 (0·8, 15·3)
Age > 50 years	2·2 (0·1, 45·0)
Non-colonic focus	0·7 (0·1, 4·5)
Absence of *Enterococcus faecalis**	0·9 (0·3, 2·9)
Appropriate antibiotic coverage	0·05 (0·003, 0·6)

Values in parentheses are 95 per cent confidence intervals. *In the initial septic focus. APACHE, Acute Physiology And Chronic Health Evaluation

Table 4 Clinical and bacteriological differences in 123 patients with or without a postoperative enterococcal infection who were treated with cefotaxime plus metronidazole

	Postoperative enterococcal infection		
	Present (*n* = 22)	Absent (*n* = 101)	*P*§
Age (years)*	71·1(12)	57·4(21)	0·002
APACHE II score*	11·6(4)	7·8(5)	0·004
Elebute score*	11·4(4)	8·5(4)	0·009
Type of infection†			0·0001
Abscess (*n* = 31)	6 (19)	25 (81)	
Secondary peritonitis (*n* = 78)	8 (10)	70 (90)	
Postoperative peritonitis (*n* = 14)	8 (57)	6 (43)	
Anatomical site†			0·04
Colon (*n* = 42)	11 (26)	31 (74)	
Hepatobiliary (*n* = 13)	4 (31)	9 (69)	
Small bowel (*n* = 14)	4 (29)	10 (71)	
Gastroduodenal (*n* = 14)	1 (7)	13 (93)	
Appendix (*n* = 38)	2 (5)	36 (95)	
Enterococcus faecalis‡ (present : absent)	10 : 12	14 : 87	0·003
Pseudomonas aeruginosa‡ (present : absent)	11 : 11	15 : 86	0·0009
Mean no. of different species‡	2·8	2·2	0·03
Mortality†	6 (27)	3 (3)	0·0001

*Values are mean(s.d.). †Values in parentheses are percentages. ‡Isolated from the initial sample. APACHE, Acute Physiology And Chronic Health Evaluation. §Student's t and χ^2 tests appropriate drugs against these micro-organisms[4,19–23]. This occurs, despite the fact that two decades ago the prognostic relevance of enterococcal bacteraemia was highlighted[24] and that enterococci are often quoted as a cause of treatment failure[4,21]. There is increasing consensus that these are associated with lack of appropriate antibiotic coverage of micro-organisms present in the abdomen when empirical antibiotic therapy is initiated[4,22,25–27]. Two trials have shown similar success rates when comparing piperacillin or tazobactam with combination antibiotic therapy[8,18]. However, lack of power and over-representation of patients with appendicitis or cholecystitis in these studies render the results regarding the role of enterococci difficult to interpret. The present findings support the concept that

Table 5 Clinical and bacteriological differences between patients with or without postoperative enterococcal superinfection, excluding perforated appendicitis

	Superinfection (n = 16)	No superinfection (n = 94)	P§
Age (years)*	72·4(10)	63·1(13)	0·01
APACHE II score*	12·4(4)	10·2(5)	0·04
Elebute score*	11·4(5)	9·7(4)	n.s.
Type of infection			n.s.
Abscess	5 (15)	29 (85)	
Secondary peritonitis	8 (14)	52 (86)	
Postoperative peritonitis	3 (19)	13 (81)	
Antibiotics used†			0·01
Cefotaxime + metronidazole	11 (69)	54 (57)	
Carbapenems	5 (31)	12 (13)	
Piperacillin–tazobactam	0 (0)	28 (30)	
Pseudomonas aeruginosa†‡	5 (31)	7 (8)	0·005
Candida albicans†‡	0 (0)	17 (18)	n.s.
Mean no. of different species‡	2·8	2·1	0·03
Mortality†	4 (25)	7 (7)	0·03

*Values are mean(s.d.). †Values in parentheses are percentages. ‡Isolated from the same initial sample. APACHE, Acute Physiology And Chronic Health Evaluation; n.s., not significant. §Student's t and χ^2 tests

Table 6 Clinical and bacteriological differences between survivors and non-survivors

	Non-survivors (n = 14)	Survivors (n = 186)	P¶
Age (years)*	73·2(14)	58·5(19)	0·006
APACHE II score*	13·2(5)	8·2(5)	0·004
Elebute score*	14·0(5)	8·9(4)	0·0001
Primary infection†			n.s.
Abscess (n = 53)	3 (6)	50 (94)	
Secondary peritonitis (n = 113)	7 (6)	106 (94)	
Postoperative peritonitis (n = 34)	4 (12)	30 (88)	
Anatomical site†‡			n.s.
Colon (n = 67)	8 (12)	59 (88)	
Hepatobiliary (n = 33)	2 (6)	31 (94)	
Small bowel (n = 22)	1 (5)	21 (95)	
Gastroduodenal (n = 27)	3 (11)	24 (89)	
Appendix (n = 49)	0 (0)	49 (100)	
Postoperative infectious complication†	12 (86)	83 (45)	0·003
With *Enterococcus faecalis*§	7 (50)	27 (15)	0·07
With Enterobacteriaceae	5 (36)	39 (21)	n.s.
With *Pseudomonas aeruginosa*	1 (7)	22 (12)	n.s.
With fungi	2 (14)	17 (9)	n.s.

*Values are mean(s.d.). †Values in parentheses are percentages. ‡Focus of infection was not precisely defined in two patients. §Percentage of patients with an infectious complication involving this micro-organism. APACHE, Acute Physiology And Chronic Health Evaluation; n.s., not significant. ¶Student's t and χ^2 tests when *E. faecalis* is present in the initial sample and is not covered by the antibiotics given, about 40 per cent of the patients are expected to develop a postoperative enterococcal infection. This means that, with the possible exception of perforated appendicitis, in which *E. faecalis* was never present at the time of initial surgery, patients with complicated intra-abdominal infections should receive coverage against the enterococci with a β-lactam agent. This is particularly true for patients with postoperative peritonitis in whom enterococci are isolated in roughly half of the episodes.

As reported previously[12], the presence of enterococci in the primary septic focus as well as in postoperative infections is associated with a worse disease severity score. Overall, a 35 per cent postoperative infection rate involving enterococci was observed in patients with an APACHE II score of 10 or more, whereas only 7 per cent of the less ill patients had an enterococcal postoperative infection. When perforated appendicitis was excluded from the analysis, the APACHE II score and mortality rate were still significantly worse for patients with enterococcal superinfection. Thus, surgeons should be aware that the presence of a postoperative enterococcal infection is a marker of severe disease and is associated with a worse outcome.

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Correspondence

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Tumour location and the effects of preoperative radiotherapy in the treatment of rectal cancer (*Br J Surg* 2001; 88: 839–43)

Sir

The conclusion that preoperative radiotherapy should be used with total mesorectal excision surgery is debatable. Preoperative irradiation reduces local relapse as shown by Frikholm *et al.*[1]. The concerns with this preoperative approach are about irradiating patients with Dukes' A lesions as well as patients with metastatic disease. Patients in these categories can be identified by endoluminal ultrasonography and/or a computed tomography scan of the liver and lungs. This would reduce the unnecessary use of radiotherapy in these patients. Moreover, since combination radiochemotherapy is usually the norm in the postoperative setting (depending on the Dukes' classification), it is also important to await the European Organization for Research on Treatment of Cancer 22921 trial comparing preoperative radiotherapy with combination preoperative chemoradiotherapy. As stated by the authors, the results of the Dutch trial[2] comparing total mesorectal excision with or without radiotherapy are eagerly awaited. I would urge discretion in recommending the routine use of preoperative radiation with the data and results presented in this paper.

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Doctors and the law – a personal view (*Br J Surg* 2001; 88: 1025–6)

Letter 1

Sir

It would be a sad day for British surgical practice if the advent of defensive medicine (to which the author alludes) were to result in atrophy of risk profiling – that most important of all clinical decision skills. This tailors interventional treatment appropriately, taking account of the fact that even time-honoured risk factors, such as increasing age, are not absolute. These can be favourably modified by timely surgical intervention, as shown in the management of bleeding peptic ulcer in people aged over 60 years[1]. Crucial to the issue of informed consent is the extent to which interventional risks as well as contraindications should be operator specific as opposed to being procedure specific. This is an issue of fundamental relevance to all operator-dependent interventional modalities, be they diagnostic, as in radiological practice, or therapeutic, as in surgical practice.

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Letter 2

Sir

Dr Johnson's leader does not provide a historical perspective and it neglects the patient's voice. 'How times change' laments Dr Johnson – only a few years ago we could commit errors and 'in the event of an adverse settlement a doctor's indemnity insurance paid up and life went on … never even discovering how the case was concluded'. Didn't we want to know? Dr Johnson paints a picture where doctor's are victimized by patients (always frivolous complaints?), administrators, lawyers and even nasty journalists. I would like to refer the author to an excellent recent article 'American medical malpractice litigation in historical perspective'[1]. Clearly, the intensity of legal onslaught on doctors followed the gradual demise of professional elitism, the increase in health-awareness of the 'masses' (and diminished 'passivity'), and the improvement in medical care. The latter may sound paradoxical but 'there cannot be malpractice without established practice'[1].

Times are changing indeed. No more can one expect the patient to follow commands. Patients want to be better informed and us to be accountable. Finally, where is the patient's voice? Shouldn't we admit that doctors are unwittingly and accidentally harming a certain percentage of patients? Shouldn't harmed patients be compensated? Should their doctors be disciplined? As we know, when the medical profession fails to control itself, administrators, lawyers and journalists enter the vacuum. Alas, time has changed.

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Portsmouth POSSUM models for abdominal aortic aneurysm surgery (*Br J Surg* 2001; 88: 958–63)

Sir

Our experience at the Norfolk and Norwich Hospital did not show any correlation between the Portsmouth Physiological and Operative Severity Score for enUmeration of Morbidity and mortality (P-POSSUM)[1] and the 30-day mortality rate following elective abdominal aortic aneurysm (AAA) operations. Ninety-five patients underwent elective AAA surgery between 1996 and 1998, and there were 11 deaths (11·6 per cent). Mean P-POSSUM scores were 7·22 (range 1–33·1) for the whole group and 9·47 (range 4–15·2) for the non-survivors. P-POSSUM did not correlate with 30-day mortality in the two groups above and below mean POSSUM and there was no correlation with individual scores either. Individual parameters such as blood pressure, blood loss, renal and pulmonary function correlate with postoperative death[2,3]. Our results suggest that the sum of such factors as represented by P-POSSUM is inaccurate in predicting mortality following elective AAA surgery. A recent paper with a similar data set has shown some correlation[4].

The authors did not refer to Lazarides *et al.*[5] who showed that Acute Physiology And Chronic Health Evaluation II and P-POSSUM scores did not correlate with outcome after emergency AAA surgery. Their assumption that P-POSSUM is a useful predictor of outcome following vascular surgery in general is contradicted by others[6]. The authors' concept of refashioning the equation to be more specific to elective/emergency AAA surgery seems appropriate and the larger number of observations support the hypothesis adequately, at least for elective AAA surgery.

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Author's reply

Sir

The most important conclusion of our study was that a separate, distinct model is required for patients with ruptured abdominal aortic aneurysm (AAA). Ruptured AAAs could not be described by a model that covers most vascular surgery. The need for distinct models for particular operations, or the patients requiring them, has been demonstrated elsewhere[1–4]. Importantly, following the Portsmouth Physiological and Operative Severity Score for enUmeration of Morbidity and mortality (P-POSSUM) methodology, the POSSUM data items could still be used to generate an appropriate risk model.

We found that the mortality of patients undergoing elective AAA repair in our data set could be successfully described using both the Vascular Surgical Society of Great Britain and Ireland POSSUM[5] risk model and the P-POSSUM[6] model for general surgery. This is not to say that either of these is the most appropriate model for elective AAAs. As more data are collected and aggregated (for example by the Vascular Surgical Society of Great Britain and Ireland) a more accurate model is likely to be developed.

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Randomized study comparing cardiac response in endovascular and open abdominal aortic aneurysm repair (*Br J Surg* 2001; 88: 1059–65)

Sir

The study by Cuypers *et al.* demonstrates that endovascular repair (EVAR) is associated with fewer silent myocardial ischaemic episodes than open repair but haemodynamic and physiological stress cannot fully explain this disparity. The brief period of ischaemia in EVAR is associated with less systemic inflammatory response. The pro-inflammatory response initiated during surgery continues in the postoperative period and contributes to an increased risk of myocardial ischaemia. The majority of events that constitute the acute coronary syndrome are related to plaque rupture or ulceration[1]. These vulnerable plaques tend not to be at sites of high-grade stenoses that cause stable angina or rate-related ischaemia. Consequently the regions at risk of postoperative myocardial ischaemia might be different from those of rate-related ischaemia. Both stress and pro-inflammatory cytokines are capable of disrupting these vulnerable plaques. A smaller inflammatory response in the EVAR group may explain the lower frequency of ischaemic events in that group.

Recent experiments have demonstrated that brief periods of ischaemia before a prolonged insult are capable of markedly reducing the extent of tissue injury, a process known as ischaemic preconditioning[2]. The question that arises is: are these periods of silent ischaemia beneficial by eliciting ischaemic preconditioning?

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Author's reply

Sir

Dr Rittoo raises an important point. Up to 50 per cent of myocardial ischaemia is not related to haemodynamic stress and is therefore referred to as 'non-demand' ischaemia[1]. At no point have we suggested an exclusive correlation between the observed reduction of haemodynamic stress and a lower incidence of myocardial ischaemia in the endovascular repair group. There is no doubt that a more stable haemodynamic situation is less likely to compromise the balance between myocardial oxygen demand and supply[2]. Other factors not related to haemodynamics, for example inflammatory mediators, may have an effect. We thank Dr Rittoo for underscoring this point to avoid any possible misinterpretation.

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P. J. Morris (ed.)

284 × 218 mm. Pp 787 Illustrated 2001 Philadelphia, Pennsylvania WB Saunders £148·00.

This is undoubtedly the most authoritative textbook written about renal transplantation. It has become the standard reference book on the subject and the arrival of the fifth edition will be widely welcomed by the international transplant community. There have been many new developments, both in the clinic and laboratory, during the 6 years since the last edition was published and the book has expanded significantly to reflect this. It now extends to some 43 chapters covering all aspects of renal transplantation but, despite this, remains an easily manageable size. A little over half of the chapters are by UK-based authors and many of these are from the editor's own centre in Oxford. The remaining chapters are mostly from authors in North America and Australasia. All of the contributors are acknowledged experts in their field and have produced, without exception, carefully written, well illustrated and extensively referenced chapters. Most chapters have undergone major revision since the last edition and several completely new chapters have been added. There are, for example, new chapters on dialysis access, chronic rejection and liver disease in renal transplant recipients. The newer immunosuppressive agents such, as tacrolimus, mycophenolate mofetil and sirolimus, which were grouped together in a single chapter in the previous edition, now have individual chapters devoted to them. Other new chapters reflect recent developments, such as laparoscopic donor nephrectomy and renal xenotransplantation. In short, this book seems set to retain its position as the premier text on renal transplantation for the foreseeable future.

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Integrated Basic Surgical Sciences

J. Toouli, C. Russell, P. Devitt and C. Ingham Clark

280 × 198 mm Pp. 843 Illustrated. 2000 London: Arnold £96·00.

In the preface the editors emphasize that medical education has changed towards problem-solving learning and that surgical teaching should follow the same direction. The book is divided into two parts. The first addresses 55 clinical problems summarized in 23 chapters and covers the most common surgical problems. In some chapters the problem-oriented approach is used consistently, for example chapter 11 about dysphagia, where a case history, the clinical features of several diagnoses, further investigations and management are described. However, in other chapters, for example chapter 13 about jaundice, a more traditional approach has been used, describing the pathophysiology of jaundice and a short summary of different causes of obstructive jaundice. Despite the variations in the 'problem-solving approach' in the different chapters, this is the first surgical book focusing primarily on the clinical problem. This might be a step forward in the education of students and surgical trainees.

It is also appreciated by the authors that, while this problem-oriented approach is helpful for teaching the appropriate diagnostic evaluation of an individual patient, more basic knowledge of various areas of surgical practice should be provided. The second part, entitled 'Clinical Practice', therefore includes chapters covering different areas of surgery, such as traumatology, oncology, radiological investigations, motility disorders, preoperative assessment, postoperative care and use of surgical tools. The combination of problem-solving and clinical practice in one book is stimulating.

The text is clearly presented and illustrated by useful tables and figures. The 'further reading' provided in most chapters refers generally to relatively old literature. Contributing authors are geographically selected from Australia, New Zealand and the UK, and this book is a 'must' for surgical students following surgical basic training in these countries. However, it will also be of use in other European countries, especially those that are currently developing a similar type of basic surgical training programme. This volume is also of interest to students in general, particularly those who have problem-based learning curricula.

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General Surgical Operations. 4th ed.

R. M. Kirk

280 × 225 mm Pp. 903 Illustrated 2000 Edinburgh Churchill Livingstone £102·00.

This book probably needs little introduction as it first appeared in 1978. A book about surgical technique making it to the age of 23 years means it has met great success over time and it has been constantly updated to keep up with the continuously growing body of surgical knowledge. This most recent edition incorporates significant surgical innovations such as laparoscopic procedures and intraoperative colonic lavage. As Mr Kirk puts it, 'emphasis is given to unexpected findings during surgery and to difficulties that may arise when dealing with crucial steps of the operations most commonly performed by general surgeons'. This is not a text of surgical anatomy or a text displaying procedures step by step. It is a book on surgical tactics, important manoeuvres and tricks, highlighted by an accompanying concise text with black and white schematic drawings illustrating key technical issues. It may well be an essential reference text for candidates sitting for fellowship of the surgical colleges of Great Britain and Ireland, and for surgeons in training worldwide. It is also aimed at the truly general surgeon who faces emergency or even elective procedures in situations in which there is no recourse to specialized units.

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Essential Surgical Practice. 4th ed. Vol 1.

A. Cuschieri, R. Steele and A. R. Moosa

275 × 200 mm. Pp. 585. Illustrated. 2001. London: Arnold. £65·00.

Since the last edition which was published in 1995 the surgical training curriculum in the UK and many other countries has undergone radical revision, with the introduction of basic and higher surgical training. To reflect this the previous large single volume has been split into a basic surgical training book in the generality of surgery (volume 1) and an advanced surgery book (not reviewed). Chapters have been replaced by holistic topic modules. So, for example, the module on 'the patient with cancer' includes basic science and the principles (as applied to all cancers) of investigation, staging, screening and adjuvant therapy, and is referenced to modules on quality-of-life assessment and palliative care. Important new subjects, previously not well covered, include legal considerations, audit and professional development and these have a specific module. This rearrangement works well; the editors have minimized duplication. It also complements the format of the distance learning programmes used by many colleges. The text is internally cross-referenced but the articles listed at the end of each module are not cited within the text. This will not help trainees wishing to read further and could be revised. The book is well illustrated with radiographs and diagrams, but some clinical photographs have not reproduced well. Volume 1 of this new edition maintains the high standard of its predecessors and will serve basic surgical trainees well. I have little doubt it will remain a popular reference book, and rightly so.

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Surgery of the Liver and Bilary Tract. 3rd ed.

L. H. Blumgart and Y. Fong

280 × 220 mm. Pp. 2244. Illustrated. 2000. Philadelphia, Pennsylvania: WB Saunders. £305·00.

This is the third edition of this extremely detailed and useful text. It has increased in size considerably from the second edition and the additional chapters enhance it significantly. Furthermore, the CD-ROM illustrating some key surgical procedures is extremely useful. The introduction of colour photographs is a great improvement. This text has become the standard for trainees in hepatobiliary and upper gastrointestinal surgery; it is also a reference for practising hepatobiliary surgeons. The new edition will ensure that it maintains this position.

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Principles of Surgical Management

C. Quick and P. Thomas

283 × 230 mm. Pp. 638. Illustrated. 2001. Oxford: Oxford University Press. £79·50.

This book of over 600 pages concerns the management of surgical patients. It is written by a general and vascular surgeon (C. Quick) and a general and colorectal surgeon (P. Thomas). The illustrations are by Philip Deakin and are extremely well done. The vast majority of the authors are British; a few are from Ireland and Australia. One might suspect the book to be somewhat restricted to current British opinions, but this is not the case: it is very world oriented and up to date.

The volume starts with an interesting chapter on informed consent, medical negligence and screening of populations, all very well handled. Most impressive is the chapter 'Avoiding hazards in the theatre'; the pitfalls of positioning the anaesthetized patient are complete and highlighted with marvellous illustrations. Other chapters deal with co-morbidity, infection, nutrition, blood transfusion and pain. In the chapter on laparoscopic techniques, living donor nephrectomy is not mentioned at all; this should be added in the next edition. As might be expected from the specialization of the authors, the chapters on vascular and colorectal surgery are comprehensive and beautifully illustrated. At the end there are chapters on (para)thyroid surgery, salivary glands, breast cancer and hernias. They do not fit well with the concept of the book and the more specific textbooks on these topics provide better information. Still, this new book presents an impressive amount of information for surgical residents and surgeons (and maybe also for medicolegal experts). Finally, the drawings in black and green are very good and ideal for teaching purposes. This book belongs on the shelf of every teaching hospital.

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Hepatobiliary and Pancreatic Surgery. 2nd ed: A Companion to Specialist Surgical Practice. 2nd ed.

O. J. Garden (ed.)

250 × 190 mm Pp. 475. Illustrated 2001. Philadelphia, Pennsylvania: WB Saunders £59 95.

This book is targeted mainly at the higher surgical trainee and the busy practising surgeon. It would also serve as a useful guide for candidates preparing for advanced fellowship of the Royal College of Surgeons examinations. However, it lacks the detail required of a reference book, although the bibliographies after each chapter are quite authoritative. The format and open style of the layout facilitates browsing for specific topics, and the pictures and photographs are adequate though lacking colour, presumably to minimize cost. This book deals more with general strategy and management algorithms rather than the detailed technique of surgery or endoscopic treatment. It tries its best to give a fair and balanced view of conflicting or rival strategies practised by different centres. The authors attempt to be evidence-based and make a deliberate point of rating data and conclusions on the basis of their scientific veracity. High-value conclusions and studies are marked with the symbol of a scalpel.

The information is relatively up to date, taking into account that textbooks generally take a few years to write and that the field continues to progress during the time of production. Nevertheless, most chapters deal with the latest technology and methods. An example is the current discussion on the management of common bile duct stones, comparing the rival endoscopic and laparoscopic approaches. On the other hand the chapter omits any discussion of intraoperative endoscopic retrograde cholangiopancreatography. Other omissions are the failure to mention laparoscopic approaches in resection of the liver and pancreas. I would have liked a more extensive discussion of three-dimensional reconstructive technology of computed tomography, magnetic resonance imaging and angiographic images as these are developing at a rapid rate and pictures of these amazing techniques should have been included. The authors are mainly of English or Commonwealth origin, with the addition of two French contributors. There are no American contributors or (apart from the French) any from non-English-speaking countries. Although many of the writers are internationally known authorities, this field also has many experts in Japan, Germany, Hong Kong and Taiwan who have made significant contributions in the past two decades. The authors do, however, try to some degree to make reference to their work either in the text or in the bibliography. The Sugiura procedure for treatment of variceal bleeding, for instance, is mentioned, albeit briefly.

Some bias is inevitable, however, as in the section on injection sclerotherapy where Johnston's pioneering work is clearly shown in bold print whereas Paquet, who first used the flexible gastroscope for variceal sclerotherapy, appears only in the bibliography. It is well known that the flexible scope subsequently became the dominant mode of access for three decades. Recurrent pyogenic cholangitis, a big problem in the Orient, merits only one page, and the important percutaneous and endoscopic techniques pioneered by Ker, Yamakawa and others are not mentioned. These minor criticisms aside, the book is generally a good read and a decent overview of the field. I recommend it, especially to the surgeon in training in Western countries and Australia, and to those of other countries who participate in a British-style training and examination system.

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Scientific Surgery

The *BJS* is committed to the practice of surgery based on scientific evidence. Each month we will publish a list of randomized trials and meta-analyses collated from English-language publications. A collection of all these papers will be available in the Scientific Surgery archive which will be held on the *BJS* website together with links to free Medline sites where the full papers can be accessed (see below for details). If you have recently published a randomized trial that has not been featured in Scientific Surgery, the Editors would be pleased to receive a reprint and consider its inclusion.

Nilsell K, Thorne A, Sjostedt S, Apelman J, Pettersson N. Prospective randomised comparison of adjustable gastric banding and vertical banded gastroplasty for morbid obesity. *Eur J Surg* 2001; **167:** 504–9.

Weight loss and complications were similar in both groups in this trial including 59 patients, but reoperation within 5 years was needed significantly more often after vertical banded gastroplasty (11 of 30 *versus* three of 29).

Chrysos E, Tzortzinis A, Tsiaoussis J, Athanasakis H, Vasssilakis J, Xynos E. Prospective randomized trial comparing Nissen to Nissen–Rossetti technique for laparoscopic fundoplication. *Am J Surg* 2001; **182:** 215–21.

Division of the short gastric vessels (Nissen–Rossetti) had no impact on clinical outcome but prolonged the operation and increased the risk of gas bloat (13 of 24 *versus* nine of 32; $P = 0{\cdot}02$) in the 56 patients included.

Robinson A, Thompson DG, Wilkin D, Roberts C. Guided self-management and patient-directed follow-up of ulcerative colitis: a randomised trial. *Lancet* 2001; **358:** 976–81.

A total of 203 patients enrolled. Relapses were treated more quickly in the group with patient-directed follow-up (difference was a mean of 35 h, 95 per cent confidence interval 16·4 to 60·2 h). This group also had significantly fewer visits to the hospital and general practitioner surgery.

Merli G, Spiro TE, Olsson CG, Abildgaard U, Davidson BL, Eldor A *et al.* Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med* 2001; **134:** 191–202.

A total of 900 patients were treated in three groups. Enoxaparin, either once or twice daily, was as effective as heparin: major haemorrhage rates (1·3–2·1 per cent) and the incidence of recurrent thromboembolism (2·9–4·4 per cent) were similar in all groups.

Mosorin M, Juvonen J, Biancari F, Satta J, Surcel HM, Leinonen M *et al.* Use of doxycycline to decrease the growth rate of abdominal aortic aneurysms: a randomized, double-blind, placebo-controlled pilot study. *J Vasc Surg* 2001; **34:** 606–10.

This small pilot study included 32 subjects with an aneurysm over 30 mm in diameter. Over 18 months, the aneurysm growth rate was reduced by a 3-month course of antibiotic.

Myrvold HE, Lundell L, Miettinen P, Pedersen SA, Liedman B, Hatlebakk J *et al.* The cost of long-term therapy for gastro-oesophageal reflux disease: a randomised trial comparing omeprazole and open antireflux surgery. *Gut* 2001; **49:** 488–94.

Some 298 patients were included. Medical therapy was cheaper over the first 5 years, except in Finland. The addition of indirect costs, such as sick leave, increased the difference in favour of omeprazole.

Mahmud N, Kamm MA, Dupas JL, Jewell DP, O'Morain CA, Weir DG *et al.* Olsalazine is not superior to placebo in maintaining remission of inactive Crohn's colitis and ileocolitis: a double blind, parallel, randomized, multicentre study. *Gut* 2001; **49:** 552–6.

The study recruited 328 patients with quiescent Crohn's disease. Olsalazine failed to reduce the relapse rate or the time to relapse, but had a significant number of adverse gastrointestinal side-effects.

Prager M, Polterauer P, Bohmig HJ, Wagner O, Fugl A, Kretschmer G *et al.* Collagen *versus* gelatin-coated Dacron *versus* stretch polytetrafluoroethylene in abdominal aortic bifurcation graft surgery: results of a seven-year prospective, randomized multicentre trial. *Surgery* 2001; **130:** 408–14.

A total of 315 patients were included in a three-way trial. Five-year patency rates were similar (89–92 per cent), but the graft infection rate was higher with Dacron (3 per cent) than polytetrafluoroethylene (0 per cent), ($P < 0{\cdot}03$).

Ohwada S, Satoh Y, Kawate S, Yamada T, Kawamura O, Koyama T *et al.* Low-dose erythromycin reduces delayed gastric emptying and improves gastric motility after Billroth I pylorus-preserving pancreaticoduodenectomy. *Ann Surg* 2001: **234:** 668–74.

Low-dose erythromycin given for 14 days after operation reduced delayed gastric emptying by 75 per cent in this study including 31 patients.

Couturaud F, Julian JA, Kearon C. Low molecular weight heparin administered once *versus* twice daily in patients with venous thromboembolism: a meta-analysis. *Thromb Haemost* 2001; **86:** 980–4.

Meta-analysis of five studies including 1522 patients failed to find any advantage for twice-daily administration in terms of recurrent deep vein thrombosis, death or bleeding complications.

The *BJS* website can be found at www.bjs.co.uk. In addition to details of current and previous articles featured in Scientific Surgery, the website contains details of the Editorial Team and Board, instructions to prospective authors, links to other sites (such as The Cochrane Library) and forthcoming surgical events. The Editors welcome comments and suggestions about the website, either in writing or through the website address.

Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland abstracts

The following abstracts were presented at the annual scientific meeting of the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland on 13–14 September 2001. The *BJS* prize was awarded to the abstract entitled 'Risk adjustment in oesophagogastric surgery: a comparison of Bayesian analysis and logistic regression' by P. P. Tekkis, H. M. Kocher, N. Kessaris, J. Poloniecki, D. Prytherch, S. S. Somers, P. McCulloch, J. P. M. Ellul and A. C. Steger.

Prospective comparison of modern imaging modalities in the diagnosis and staging of pancreatic and periampullary tumours

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Background: The aim was to compare prospectively the performance of transcutaneous ultrasonography (TUS), triple-phase spiral computed tomography (spCT), gadolinium-enhanced magnetic resonance imaging (MRI) and radial endoscopic ultrasonography (EUS) in the evaluation of patients with suspected pancreatic or periampullary tumours.

Methods: Seventy consecutive patients referred with a suspected diagnosis of pancreatic or periampullary tumour were imaged with TUS, spCT, MRI and EUS. The results were correlated with histology for diagnosis, lymph node (LN) metastases and liver metastases, and with surgical findings for involvement of the portomesenteric venous (PV/SMV) system. Paired comparisons were performed by McNemar's test or by the paired sign test if the number of unmatched pairs was less than ten.

Results: Overall tumour detection by TUS, spCT, MRI and EUS was 74, 64, 75 and 87 per cent respectively. When the size of the tumour in the resected specimens was measured, the rate of detection of tumours under 20 mm in diameter was 55, 45, 27 and 90 per cent by TUS, spCT, MRI and EUS respectively. The performance of each modality for the diagnosis and staging variables are shown in the *Table* below.

Conclusion: Sonographic methods are better than spCT and MRI at establishing the diagnosis in patients with suspected pancreatic and periampullary tumours. EUS was especially useful in the detection of tumours less than 20 mm in diameter. Sonographic methods were as good as spCT and MRI in staging the disease.

Table Prospective comparison of modern imaging modalities in the diagnosis and staging of pancreatic and periampullary tumours

	TUS	spCT	MRI	EUS
Diagnosis				
Sensitivity (%)	92 (46 of 50)	74 (43 of 58)	69 (37 of 54)	83 (47 of 57)
Specificity (%)	75 (3 of 4)	100 (2 of 2)	33 (1 of 3)	100 (4 of 4)
Liver metastasis				
Sensitivity (%)	38 (3 of 8)	78 (7 of 9)	67 (6 of 9)	–
Specificity (%)	97 (35 of 36)	93 (38 of 41)	92 (36 of 39)	–
LN metastasis				
Sensitivity (%)	11 (1 of 9)	33 (4 of 12)	9 (1 of 11)	27 (3 of 11)
Specificity (%)	100 (17 of 17)	84 (16 of 19)	100 (17 of 17)	95 (18 of 19)
PV/SMV involved				
Sensitivity (%)	73 (11 of 15)	53 (9 of 17)	73 (11 of 15)	88 (14 of 16)
Specificity (%)	94 (15 of 16)	100 (19 of 19)	94 (16 of 17)	78 (14 of 18)

Paired comparisons found the only significant differences were for diagnosis: TUS was significantly better than spCT ($\chi^2 = 5{\cdot}33$, 1 d.f., $P < 0{\cdot}02$) and EUS was significantly better than MRI ($\chi^2 = 5{\cdot}56$, 1 d.f., $P < 0{\cdot}02$)

Transoesophageal endoscopic plication *versus* Nissen fundoplication for gastro-oesophageal reflux disease

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Background: Endoscopically performed suturing techniques for the treatment of gastro-oesophageal reflux disease are currently being evaluated. In this study transoesophageal endoscopic plication (TEP) was compared retrospectively with conventional Nissen fundoplication.

Methods: Nineteen patients had TEP and were compared with 24 patients who had Nissen fundoplications less than 12 months after surgery. All patients underwent manometry, endoscopy, 24-h monitoring and symptom severity scoring before and after the procedure.

Results:

	Nissen fundoplication		TEP	
	Preop.	Postop.	Preop.	Postop.
Acid score	50 (19–186)	3 (0–120)*	36 (18–141)	17 (9–166)
Sphincter pressure (mmHg)	8 (3–30)	15 (6–33)	15 (3–20)	10 (3–20)

Values are median (range). Preop., before operation; postop., after operation. *$P < 0{\cdot}01$ *versus* TEP

Symptom score, heartburn severity and frequency were significantly improved after TEP and Nissen fundoplication at a median of 3 (3–7) and 4·5 (2–14) months' follow-up respectively. Twenty-four-hour pH monitoring showed improvement in the number of episodes and percentage of time below pH 4 for TEP, but only nine of 19 patients achieved physiological control (acid score less than 15) compared with 22 of 24 for Nissen fundoplication.

Conclusion: In the short term TEP achieved similar clinical results to Nissen fundoplication. However, its efficacy in terms of achieving physiological control was substantially less. Further studies are required, including a prospective randomized trial of TEP *versus* Nissen fundoplication.

Oesophagectomy following neoadjuvant therapy compared with resection alone is associated with increased perioperative risk and an attenuated bone marrow response

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Background: Neoadjuvant chemoradiotherapy is increasingly used in the curative approach to oesophageal cancer. This multimodality approach has attendant risks of immunosuppression which may theoretically increase operative risks, but published phase II and III studies have not focused on the perioperative period and the clinical significance remains unclear. This report highlights the lessons learned in a single surgeon's experience outside of a randomized study.

Methods: In a 6-year period 190 oesophagectomies were performed by one surgeon and all data were stored on a prospective database. Of the 190 patients, 48 had neoadjuvant chemotherapy (fluorouracil and cisplatin) and radiation therapy (40 Gy) followed by resection 4 weeks later if the neutrophil count was above $2 \times 10^6\,\mathrm{ml}^{-1}$. The white cell count, neutrophil count, platelet count and lymphocytes were measured before operation and on days 1, 3, 5 and 7 after surgery. The in-hospital mortality rate was recorded.

Results: The surgery-only and multimodal groups were well matched in terms of performance indices, age and physiological criteria. The in-hospital mortality rate in the 142 patients who underwent surgery alone was 3·5 per cent (five patients). In significant contrast ($P < 0{\cdot}05$), five patients in the multimodal group died (10·4 per cent); four of the latter patients had a complete pathological response to the neoadjuvant therapy but died from idiopathic acute respiratory distress syndrome. The lymphocyte and platelet counts were significantly decreased at all time points in patients who had multimodality treatment compared with counts in patients who had surgery only; the white cell count and neutrophil count was significantly decreased before operation and on day 3 after surgery in the multimodality group.

Conclusion: In this experience multimodality therapy was associated with an increased operative mortality rate compared with surgery only. The predominance of patients with an adverse outcome who had an excellent pathological response to the neoadjuvant approach is highlighted, as is the unclear mechanism of fatal lung injury. The data show some evidence of abnormal platelet, lymphocyte and neutrophil reserves in the multimodality group in the perioperative period, and further work should focus on assessing immunoinflammatory functional variables in patients who have received neoadjuvant therapy.

Plasminogen activation in the progression from metaplasia to carcinoma in Barrett's oesophagus

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Background: The progression of Barrett's oesophagus through increasing degrees of dysplasia to adenocarcinoma is characterized by the ability of epithelial cells to invade the basement membrane. Changes in the expression of components of the plasminogen activation (PA) system that allow increased production of plasmin are thought to have an important role in malignant cell invasion but little is known about the expression of these components in the premalignant stages of Barrett's oesophagus.

Methods: Levels of urokinase plasminogen activator (uPA), its cell-surface receptor (uPAr) and specific inhibitors (PAI-

1 and PAI-2) were determined by enzyme-linked immunosorbent assay in fresh frozen samples of normal oesophageal mucosa ($n = 23$), normal gastric mucosa ($n = 31$), non-dysplastic Barrett's oesophagus ($n = 14$), low-grade dysplasia ($n = 10$), high-grade dysplasia ($n = 10$) and oesophageal adenocarcinoma ($n = 30$).

Results: Levels of uPA increased from normal mucosa (median 0·11 ng mg protein^{-1}) through Barrett's oesophagus with dysplasia (0·39 ng mg^{-1}) to high levels in adenocarcinoma (0·94 ng mg^{-1}), with similar changes in the levels of uPAr. PAI-1 levels were higher in non-dysplastic and dysplastic Barrett's samples (median 3·0 ng mg^{-1}) than in normal mucosa (1·54 ng mg^{-1}) but less than those in adenocarcinoma (6·67 ng mg^{-1}). PAI-2 levels were higher in carcinoma (8·09 ng mg^{-1}) and dysplastic Barrett's (6·16 ng mg^{-1}) than in normal mucosa (4·77 ng mg^{-1}) and non-dysplastic Barrett's (1·66 ng mg^{-1}).

Conclusion: This is the first report of levels of PA components in Barrett's oesophagus. The increase in expression of uPA, uPAr and the inhibitors from non-dysplastic through dysplastic to carcinoma supports a role for this system in the development of the invasive capability of oesophageal cancer.

Influence of resection margins on survival for patients with resectable pancreatic cancer treated with chemoradiation or chemotherapy within the European Study Group for Pancreatic Cancer 1 study

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Background: Pancreatic cancer is associated with poor long-term survival. The role of adjuvant therapy remains uncertain. Resection margin-positive tumours (R_1) after operation represent more aggressive disease. It is uncertain whether patients with an R_1 resection should be treated in the same way as those who have had an R_0 resection (clear resection margins). The aim was to determine the relevance of resection margin status in resected pancreatic cancer.

Methods: ESPAC-1 is the largest study in resectable pancreatic cancer and assessed the roles of chemoradiation (CRT; 40 Gy + 5-fluorouracil (5-FU)) and chemotherapy (CT; weekly 5-FU/folinic acid). Randomization was stratified by resection margin status. Of 541 patients, 101 (19 per cent) had an R_1 resection. Prognostic variables were analysed by multivariate analysis.

Results: Resection margin status was confirmed as an independent prognostic factor with tumour size. Tumour grade and nodal status were only influential in the absence of resection margin status. Median survival (95 per cent confidence interval (c.i.)) was significantly reduced in patients who had an R_1 resection: 11 (9 to 16) *versus* 17 (15 to 18) months. Preliminary results showed no evidence of benefit for CRT irrespective of resection margin status. There was evidence of a survival benefit for patients having CT (median 20 *versus* 14 months; $P < 0{\cdot}001$). For R_0, CT produced a longer median survival (21 *versus* 15 months; hazard ratio (HR) 0·59 (95 per cent c.i. 0·45 to 0·78)). This difference was less apparent in the smaller R_1 subgroup (11 *versus* 10 months; HR 0·91 (95 per cent c.i. 0·53 to 1·55)).

Conclusion: Resection margin status reflects the biological variation of pancreatic cancer rather than tumour size. The magnitude of benefit for adjuvant CT is reduced in the smaller R_1 subset but is still worthwhile. Future randomized studies of adjuvant treatment should stratify by resection margin status and focus on chemotherapy regimens.

Increased mortality rate after oesophagectomy in patients receiving neoadjuvant treatment

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Background: Neoadjuvant treatments with infusional chemotherapy and/or external beam radiotherapy can lead to high rates of complete pathological response (approximately 40 per cent) and the 5-year survival rate in this subgroup has been projected to be about 60 per cent. There remain concerns, however, about increased surgical morbidity and mortality rates in these patients, and the extent to which these might influence optimistic forecasts of survival.

Methods: Between January 1999 and July 2001 two well matched and concurrent groups from 86 patients undergoing oesophagectomy were examined for postoperative morbidity and mortality. One group (54 patients) received neoadjuvant treatment (eight chemotherapy and 46 chemotherapy and radiotherapy) and the other 32 patients had surgery alone.

Results: Overall morbidity was similar in the two groups although severe pulmonary and septic complications were more common in patients receiving multimodal treatment (35 *versus* 19 per cent). There were five postoperative deaths, all of which occurred in patients who had received neaoadjuvant treatment (five of 54 *versus* none of 32; $P < 0{\cdot}05$).

Conclusion: Multimodal treatment is associated with an increased postoperative mortality rate. The anticipated improved survival from multimodal therapy needs to exceed the increased surgical mortality to justify this form of radical treatment.

Tumour microvessel count and bone marrow micrometastases in patients with gastro-oesophageal carcinoma

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Background: It has been proposed that tumour growth and metastasis are angiogenesis dependent. The aim was to establish if the tumour microvessel count (MVC) has an influence on tumour cell dissemination in patients with carcinoma of the oesophagus and oesophagogastric junction.

Methods: Tumour resection specimens from 42 patients with invasive gastro-oesophageal cancer underwent standard pathological analysis as well as immunocytochemical assessment of MVC. Using the endothelial marker anti-CD34, the area of greatest vascularity was determined and the number of neovessels was counted using a Kontron Interactive Image Analysis System (Kontron, Eching, Germany). A single bone marrow aspirate, taken from the iliac crest at the time of surgery, was assessed for the presence of bone marrow micrometastases (BMMs) by immunocytochemical analysis using cytokeratin markers CAM 5·2 and AE1/AE3; cytokeratin-positive cells were identified using light microscopy and confirmed morphologically to be disseminated tumour cells.

Results:

	BMMs (n=19)	No BMMs (n=23)
MVC*	166 (125–207)	137 (112–162)
Cell type		
Adenocarcinoma	14	19
Squamous cell carcinoma	5	4
Stage		
I/II	5	11
III/IV	14	12
R classification†		
R_1	17	10
R_0	2	13
Grade		
G1/2	11	10
G3/4	8	13

*Values are mean (95 per cent confidence interval). †$P = 0{\cdot}006$ (χ^2 test with Yates' continuity correction)

Conclusion: Microscopic residual disease (R_1) following surgical resection was associated with detection of BMMs; tumour stage, grade, cell type and MVC were not. In this study of patients with gastro-oesophageal cancer, the angiogenic status of the primary tumour was not observed to significantly affect systemic tumour cell dissemination.

Pancreatic resection: the argument against centralization

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*Royal Surrey County Hospital, Guildford, *St Richards Hospital, Chichester and †Frimley Park Hospital, Frimley, UK*

Background: Studies have suggested that all pancreatic resections should be performed in specialist pancreatic units as results from district units are inferior. The aim of this study was to assess the outcome of pancreatic resection by three consultant surgeons with a hepatopancreaticobiliary interest working in three adjacent district general hospitals.

Methods: The notes of all patients undergoing pancreatic resection performed by the three consultant surgeons since their appointment were reviewed. The surgical procedure, complications, histology and outcome were assessed.

Results: Eighty-six patients (mean(s.d.) age 59(14) years) have undergone pancreatic resection; there were 38 Whipple resections, 35 pylorus-preserving pancreaticoduodenectomies, 11 distal pancreatectomies, one total pancreatectomy and one local excision of the ampulla. Seven patients underwent vascular reconstruction (five portal vein, two superior mesenteric vein and one superior mesenteric artery) during resection. Postoperative complications necessitated reoperation in seven patients (8 per cent) and two patients developed a pancreatic fistula that closed spontaneously. There were five deaths (6 per cent) in hospital. There were 32 ductal adenocarcinomas, 14 ampullary adenocarcinomas and eight cholangiocarcinomas. A survey of specialized units in the UK has reported a reoperation rate of 6 per cent and a mortality rate of 6 per cent.

Conclusion: The results of pancreatic resection for tumours by consultants with a particular interest in pancreatic surgery in district general hospitals compare favourably with those from specialized centres.

Poor response to proton-pump inhibition is not a contraindication to laparoscopic antireflux surgery for gastro-oesophageal reflux disease.

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Background: The aim was to assess whether the response to proton-pump inhibitors (PPIs) in patients with gastro-oesophageal reflux disease (GORD) is an indicator of symptomatic outcome after surgery.

Methods: Some 151 patients (median age 45 (range 10–86) years) undergoing laparoscopic floppy Nissen fundoplication assessed their preoperative symptom relief in response to PPIs (at least double the standard maintenance dose) on a visual analogue scale. Symptomatic outcome and Visick score were assessed a minimum of 6 months (median 12 (range 6–28) months) following surgery.

Results: Patients with less than 50 per cent symptom relief from PPIs had an increased incidence of Visick 3 or 4 scores after operation (eight of 45 compared with three of 106 with symptom relief greater than 50 per cent; $P = 0.004$). Despite this, 30 of 37 patients with little or no response to PPIs (less than 25 per cent symptom relief) had excellent or good results from surgery (Visick 1 or 2).

Conclusion: A poor response to proton-pump inhibition may be seen as a relative caution, but is not a contraindication to laparoscopic antireflux surgery for GORD. Good results can be achieved in patients with little or no response to PPIs.

'No touch' radical regional resection for hilar cholangiocarcinoma: technique and outcome

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Background: The authors present an experience of increased resectability rates for hilar cholangiocarcinoma, with improved outcome, by employing the concept of a 'no touch' radical regional resection. This technique was applied for patients whose tumours were not resectable by standard surgical approaches.

Methods: Between August 1992 and August 2000, 82 patients with hilar cholangiocarcinoma (Bismuth II–IV) were assessed. Twenty-seven (33 per cent) underwent primary resection. The following principles were followed to achieve a radical regional primary resection ($n = 17$): (1) division of the bile duct within the pancreas; (2) resection of affected liver or to gain greater duct clearance; (3) resection of caudate lobe (segment 1); (4) *en bloc* regional connective tissue excision and peritonectomy; (5) regional and para-aortic lymphadenectomy; and (6) hepaticojejunostomy to individual segmental ducts within the hepatic remnant. Patients who were found to be inoperable because of bilateral portal vein involvement underwent resection as above but also bilateral resection and reconstruction of portal vein, using a principle of 'no touch' surgery ($n = 10$).

Results: There was one postoperative death in each group. The R_0 resection rate and survival was improved in the 'no touch' group; the 5-year actuarial survival rate was 45 per cent compared with 16 per cent in the other patients, despite more advanced radiological and operative staging.

Conclusion: The concept of a 'no touch' radical regional resection accepts the additional operative risk of bilateral portal vein resection, but offers an improved resectability rate and improved survival in advanced hilar cholangiocarcinoma. Operative assessment of tumour spread, and in particular vascular invasion, is difficult and this 'no touch' technique may offer improved survival rates if applied to all patients with potentially operable hilar cholangiocarcinoma.

Delays in management in patients with pancreatobiliary tumours

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Background: The aims were to confirm that delays exist in the management of patients awaiting curative surgery for pancreatobiliary malignancy, and to identify which steps in patient management might be responsible for the delay and how these delays might be reduced.

Methods: All new referrals of suspected pancreatobiliary malignancy to a pancreatic specialist in a tertiary centre were recorded prospectively over a 6-month period (1 October 2000 to 31 March 2001). After exclusion of emergency patients the following data were collected: time from first contact to clinic appointment; presence of base hospital scans at first clinic appointment; and time from booking to completion at the tertiary centre of a test or procedure (spiral computed tomography (CT) ($n = 9$), endoscopic ultrasonography (EUS) ($n = 21$), laparoscopy ($n = 7$) and definitive surgery ($n = 16$)).

Results: After the initial consultation 48 patients (41 from other hospitals) were suspected of having a tumour (pancreatic, 29; duodenal, five; periampullary, 14). Eighteen base hospital scans were not present at first clinic appointment. The median (range) wait was 12 (1–49) days for the first clinic appointment, 27 (16–34) days for spiral CT, 12 (1–37) days for EUS, 19 (1–34) days until laparoscopy and 28 (15–64) days until definitive surgery. The total wait from referral to definitive surgery was 79 (27–153) days.

Conclusion: Unacceptable delays exist in the processing of patients with suspected pancreatobiliary malignancy. Waiting times for imaging tests and operative procedures will need to be radically shortened to comply with the National Health Service Cancer Plan.

Pancreatic resection for cancer in England, 1995–2000

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Background: The aims were to determine the number of trusts in England undertaking resection for cancer of the pancreas and to examine if there is any link between case volume and mortality rate.

Methods: The Department of Health, Hospital Episodes Statistics databases for the 5 years 1995–1996 until 1999–2000 were filtered using International Classification of Diseases 10 codes to identify consultant episodes with a diagnostic coding for pancreatic cancer. Selected fields from these records were then extracted and converted into an Access database. Episodes that involved a major pancreatic resection were identified using Office of Population Censuses and Surveys 4 codes. Statistical

analysis utilized StatsDirect, version 1.9.5 (CamCode, Cambridge, UK).
Results: Some 1589 consultant episodes in which a patient underwent pancreatic resection for a malignant neoplasm of the pancreas were identified during this period, suggesting a resection rate of about 5 per cent in England. The median age of patients operated on was 63 (interquartile range 54–70) years. Eight hundred and seventy of these patients (54·8 per cent) were men and 712 (44·8 per cent) women; seven were unclassified. One hundred and eighty-one different trusts undertook one or more resections during the time period. Three trusts undertook more than 50 resections, 14 trusts between 20 and 50 resections, and 164 less than 20 resections. Data on death or discharge were available for 1319 of these episodes; there were 128 deaths, an overall mortality rate of 9·7 per cent. Logistic regression analysis was undertaken to investigate the predictive ability of case volume. This was found to be a significant covariate ($\chi^2 = 5{\cdot}7$, 1 d.f., $P = 0{\cdot}017$). The overall mortality rate in centres that performed more than 50 resections over the 5-year period was 4·7 per cent compared with 10·4 per cent in those performing fewer resections ($P = 0{\cdot}018$, χ^2 test).
Conclusion: Recent data from England show that mortality rates following resection for pancreatic cancer are directly related to case volume.

Serum amyloid A is a better early predictor of severity than C-reactive protein in acute pancreatitis

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Background: Serum amyloid A (SAA) is an early and sensitive marker of the extent of tissue trauma and inflammation, and may be of prognostic value in acute pancreatitis. The aim was to compare the early prognostic accuracy of SAA with that of serum C-reactive protein (CRP).
Methods: In a prospective multicentre trial, plasma SAA and CRP levels were measured in patients with severe and mild acute pancreatitis, and in a control group of patients with an acute abdomen. Plasma samples were collected on admission and at 6-h intervals for 48 h, 12 hourly between 48 and 72 h, then daily for 5 days. Plasma SAA was measured by a new enzyme-linked immunosorbent assay and CRP was measured by immunoturbidometry.
Results: There were 137 patients with mild and 35 with severe acute pancreatitis, and 74 controls. SAA levels were significantly higher in patients with severe than mild acute pancreatitis, on admission, 24 h or less after symptom onset and subsequently. Plasma CRP values were also significantly higher in patients with severe acute pancreatitis on admission, but they failed to distinguish mild from severe acute pancreatitis until 48 h after symptom onset. SAA levels predicted severity (sensitivity 67 per cent, specificity 70 per cent, negative predictive value 89 per cent, mean(s.d.) area under curve 0·70(0·05)) significantly better than CRP (57 per cent, 60 per cent, 84 per cent and 0·59(0·06) respectively) on admission ($P = 0{\cdot}02$) and at 24 h after symptom onset (area under curve 0·65(0·09) *versus* 0·58(0·09) respectively; $P \leqslant 0{\cdot}02$).
Conclusion: Plasma SAA is an early marker of severity in acute pancreatitis and superior to CRP on hospital admission and within 24 h of symptom onset. This study suggests that plasma SAA is clinically useful, with the potential to replace CRP in the management of acute pancreatitis.

Helicobacter pylori eradication reduces symptoms and prescribing requirements in patients with heartburn

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Background: There are concerns that *Helicobacter pylori* eradication may be detrimental in patients with reflux disease increasing both symptom severity and the use of proton-pump inhibitor (PPI) therapy. The aim was to evaluate the effects of *H. pylori* testing and eradication in a large population of patients with heartburn on maintenance acid suppression (more than three prescriptions in the year before study entry).
Methods: Some 1404 patients with heartburn as a symptom who were receiving maintenance acid suppression therapy attended community dyspepsia clinics at 0 and 6 months, underwent [^{13}C]urea breath testing to determine *H. pylori* status and received triple therapy where positive (50 per cent). Symptom assessment (0 and 6 months) using the Glasgow Dyspepsia Severity Score (GDSS) and case-note review (0, 6 and 12 months) was performed to collect prescribing data.
Results: Some 19 per cent of patients undergoing successful *H. pylori* eradication were asymptomatic (GDSS 1 or less) at 6 months compared with 7 per cent in the group who had failed *H. pylori* eradication and 4 per cent of those who were *H. pylori* negative ($P < 0{\cdot}001$, χ^2 test); 36 per cent of the successfully treated group ceased acid suppression therapy for 12 months following intervention, significantly more than those who remained *H. pylori* positive (20 per cent) or were *H. pylori* negative (16 per cent) ($P < 0{\cdot}001$, χ^2 test). There was little conversion to PPI therapy from H2RA agents and this was not significantly different between the three groups (4 per cent in all groups).
Conclusion: *H. pylori* testing and eradication in patients on acid suppression therapy with heartburn renders a small group of patients asymptomatic and results in cessation of therapy in a larger proportion of patients. It does not lead to an increase in the use of PPIs.

Risk adjustment in oesophagogastric surgery: a comparison of Bayesian analysis and logistic regression

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Background: Predictive models play a pivotal role in the provision of risk-adjusted operative mortality rates, but there is currently no consensus as to which statistical methodology best describes the oesophagogastric population. The purpose of this study was to assess the performance of two statistical techniques (logistic regression (LR) and Bayesian analysis) for risk prognostication.
Methods: A total of 1042 patients undergoing oesophageal ($n = 538$) or gastric ($n = 504$) surgery between 1994 and 2000 was used to develop O-POSSUM scoring systems based on stepwise LR and empirical Bayesian analysis. The following independent risk factors were used: age, physiological status, mode of surgery, type of surgery and staging. The models were developed and tested using an approximately 60:40 split-sample validation technique and observed to expected mortality rates were compared.
Results: The overall mortality rate in the study was 12·0 per cent (elective mortality rate 10·8 per cent and emergency mortality rate 25·3 per cent).

O-POSSUM model	Hosmer–Lemeshow statistic	c-index	Observed : expected mortality ratio
LR model	7·31	0·722	0·997
Bayesian model	27·72	0·723	1·004

Conclusion: The Bayesian model had poorer calibration (higher Hosmer–Lemeshow statistic), but both models predicted outcome equally well. Although the areas under the receiver operating characteristic curve (c-index) were similar, it was suggestive that these models should not be applied to individual patients but to group statistics instead. The choice of model would depend on the local expertise and software availability.

Benign stricture formation following oesophagectomy

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Background: Dysphagia is the main presenting symptom of oesophageal carcinoma and the aim of surgery is both to achieve cure and palliate symptoms. The aim of this study was to compare the frequency of benign stricture formation following oesophagogastric reconstruction in the left neck or the apex of the right chest.
Methods: A retrospective review of the case notes and telephone follow-up of all patients entered into an oesophagectomy database between January 1995 and December 2000 was performed. Data were analysed using the χ^2 test.
Results: Of 150 patients (106 men, mean age 63 years) who had oesophagectomy for carcinoma, 107 had a cervical and 43 had an intrathoracic anastomosis. All were completed as single-layer handsewn anastomoses with interrupted 3/0 polyglactin sutures. There was no difference in clinical leak rate (9 per cent cervical, 5 per cent thoracic), but the stricture rate was significantly less in patients who had an intrathoracic anastomosis (18 *versus* 57 per cent; $P < 0·001$).
Conclusion: In the absence of a difference in leak rate between the two types of reconstruction, if neck dissection is not required oesophagogastric anastomosis has a lower stricture rate when performed high in the chest.

Modified D_2 gastrectomy allied to surgical subspecialism

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Background: The impressive results reported following D_2 gastrectomy for carcinoma in large retrospective series from Japan have not been reproduced in randomized comparative studies from Europe, where higher morbidity and mortality rates without any survival benefit were reported following D_2 gastrectomy. The aim of this study was to compare the outcome after modified D_2 gastrectomy (preserving spleen and pancreas where possible), allied to surgical subspecialism, with that after conventional D_1 gastrectomy performed for gastric cancer by general surgeons in a large British cancer unit.
Methods: Two groups of patients were studied over a period of 10 years: a historical control group of 245 consecutive patients with gastric cancer, of whom 50 underwent a potentially curative D_1 resection (median age 69 years, 35 men; managed by five general surgeons), was compared with 200 consecutive patients, of whom 72 underwent a potentially curative D_2 resection (median age 70 years, 47

	Surgeon					
	1	2	3	4	5	6
Type of resection	D_1	D_1	D_1	D_1	D_1	D_2
No. of resections	22	17	4	3	4	72
Operative mortality (%)	14	18	0	0	0	8
5-year survival (%)	23	0	34	0	0	56

men, managed by a single surgeon with an interest in oesophagogastric cancer).

Results:

Stage of disease ($P = 0{\cdot}001$; hazard ratio (HR) 0·34 (95 per cent confidence interval 0·16 to 0·74)) and a D_1 lymphadenectomy ($P < 0{\cdot}001$; HR 0·38 (0·23 to 0·64)) were independently associated with poor survival on multivariate analysis.

Conclusion: Modified D_2 gastrectomy performed by a specialist surgeon can improve survival fivefold after R_0 resection without increasing operative morbidity and mortality rates.

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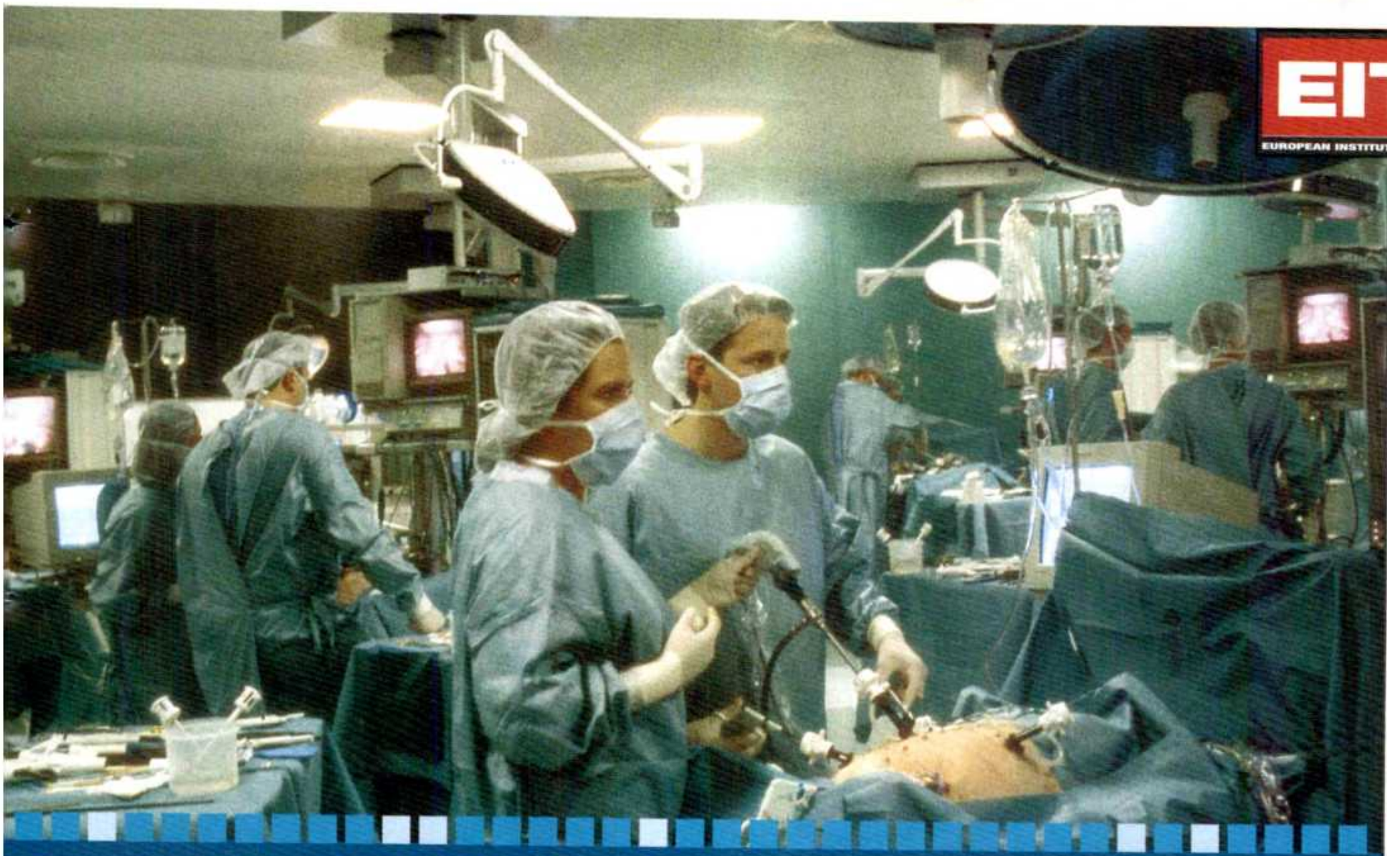

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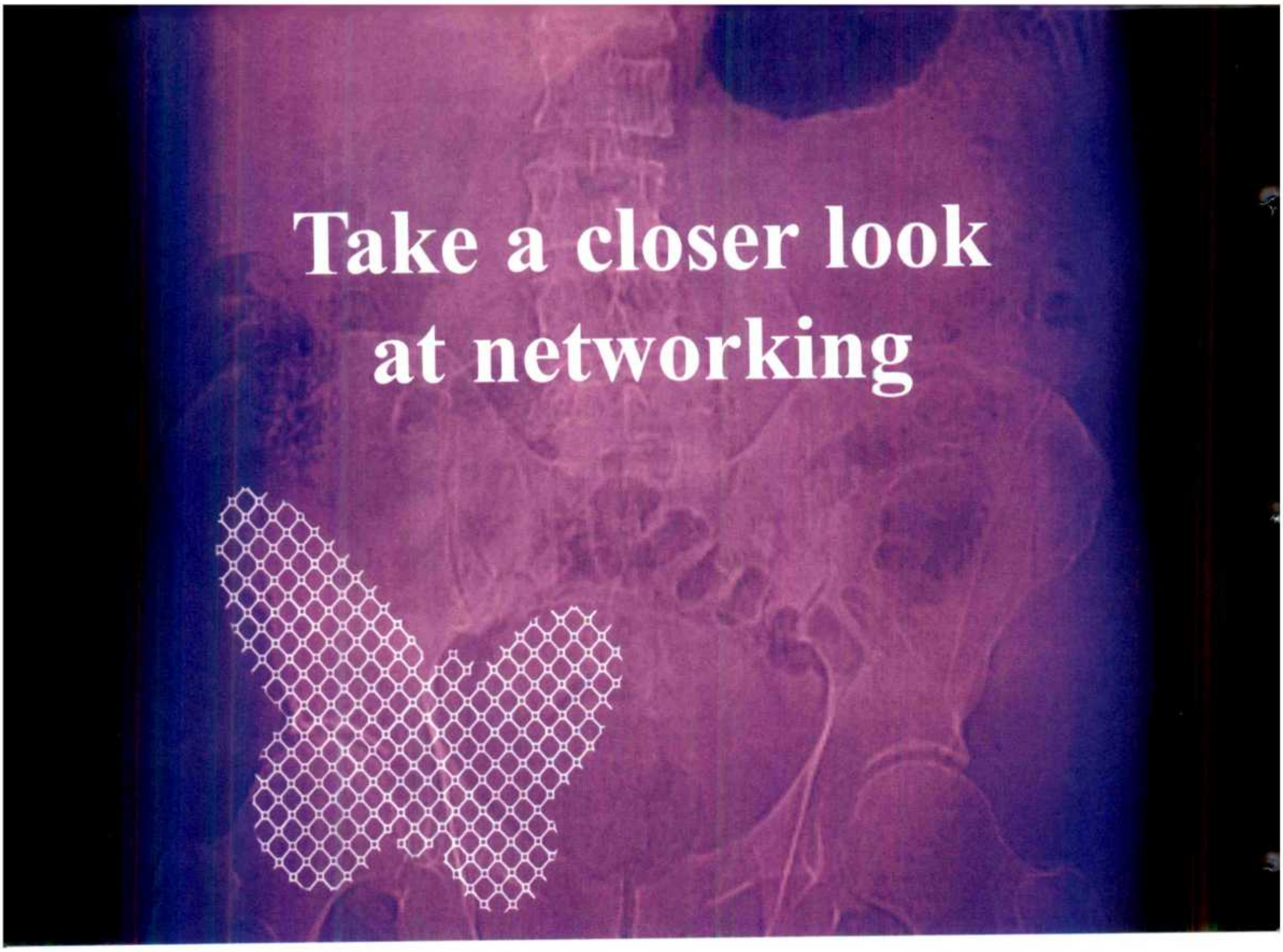

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Contents

British Journal of Surgery

Volume 89, Issue 4, April 2002

Leading articles

385 **Quality of life after repair of bile duct injury**
D. J. Gouma and H. Obertop
There is more to surgery than technical success

387 **Ecosurgery**
A. Sitges-Serra
How surgeons damage the environment

Reviews

389 **Positron emission tomography for staging and management of malignant melanoma**
R. S. Prichard, A. D. K. Hill, S. J. Skehan and N. J. O'Higgins
The indications for this useful imaging technique are discussed

397 **Acute compartment syndromes**
A. Tiwari, A. I. Haq, F. Myint and G. Hamilton
Prompt recognition and treatment are essential

Randomized trials

413 **Randomized clinical trial assessing the side-effects of glyceryl trinitrate and diltiazem hydrochloride in the treatment of chronic anal fissure**
H. M. Kocher, M. Steward, A. J. M. Leather and P. T. Cullen
Fewer headaches with diltiazem

418 **Randomized clinical trial of long-term outcome after resection of hepatitis C virus-related hepatocellular carcinoma by postoperative interferon therapy**
S. Kubo, S. Nishiguchi, K. Hirohashi, H. Tanaka, T. Shuto and H. Kinoshita
Adjuvant interferon may improve outcome after hepatic resection

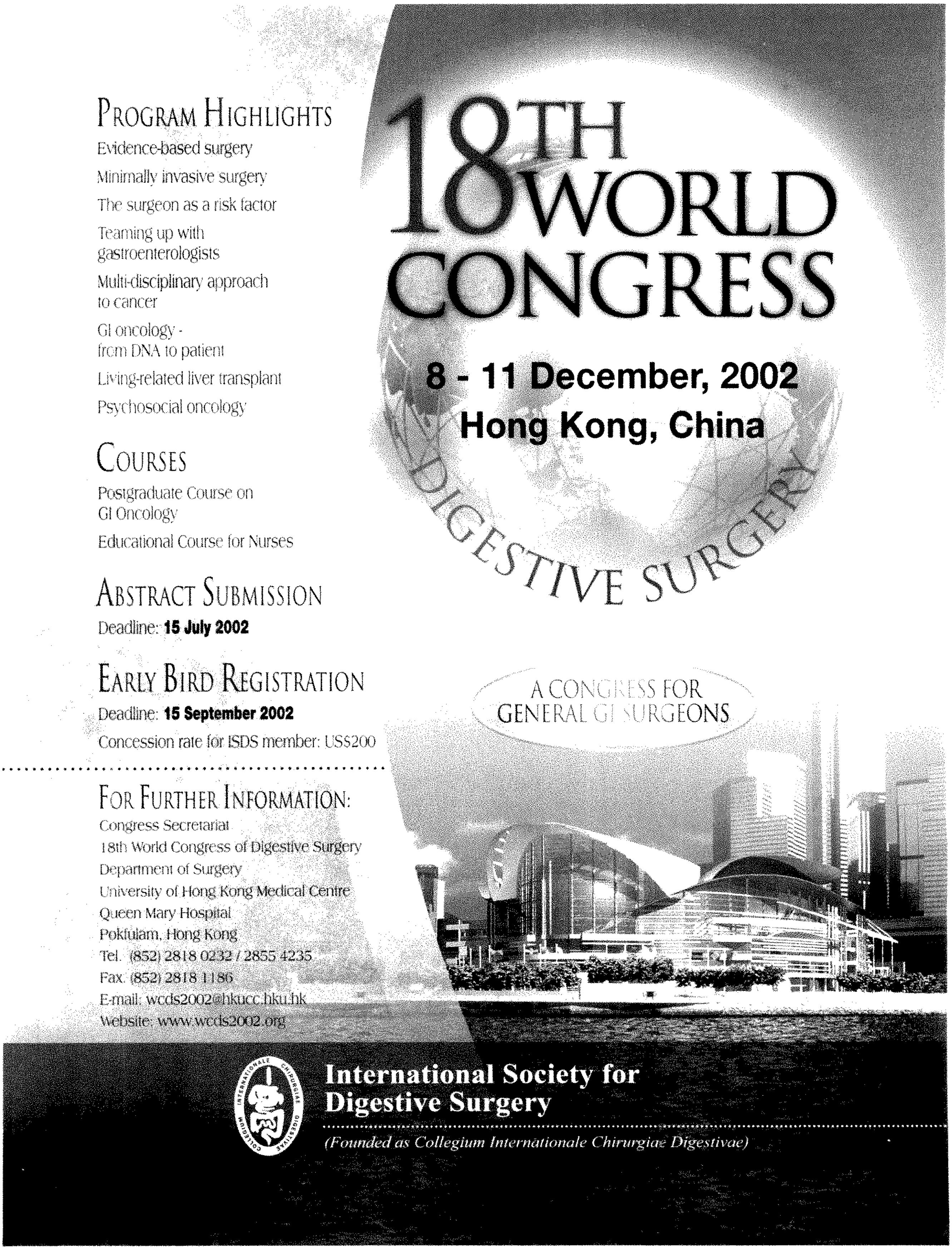
423 **Randomized clinical trial of the effectiveness of emergency day surgery against standard inpatient treatment**
P. J. Conaghan, E. Figueira, M. A. S. Griffin and C. L. Ingham Clark
Similar outcomes, costs less

428 **Randomized clinical trial of Ligasure™ *versus* conventional diathermy for day-case haemorrhoidectomy**
D. G. Jayne, I. Botterill, N. S. Ambrose, T. G. Brennan, P. J. Guillou and D. S. O'Riordain
New technique facilitates day-case surgery

Original articles

433 **Comparison of magnetic resonance cholangiography and percutaneous transhepatic cholangiography in the evaluation of bile duct strictures after cholecystectomy**
A. Chaudhary, S. S. Negi, S. K. Puri and P. Narang
Magnetic resonance cholangiography could replace percutaneous transhepatic cholangiography for this indication

437 **Uptake of Lipiodol™–cytotoxic conjugates by hepatoblastoma cells**
E. Towu, R. Al-Mufti, L. Spitz, K. Marron and M. Winslet
Lipiodol conjugatation promotes uptake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442 **Surgical repair of the ruptured thoracic and thoracoabdominal aortic aneurysms**
M. E. Lewis, A. M. Ranasinghe, M. P. Revell and R. S. Bonser
Good results in this series of 17 operations

446 **Accelerated postoperative recovery programme after colonic resection improves physical performance, pulmonary function and body composition**
L. Basse, H. H. Raskov, D. H. Jakobsen, E. Sonne, P. Billesbølle, H. W. Hendel, J. Rosenberg and H. Kehlet
Dramatic differences in postoperative parameters

454 **Fate of the rectum in patients undergoing total colectomy for Crohn's disease**
P. Cattan, N. Bonhomme, Y. Panis, M. Lémann, B. Coffin, Y. Bouhnik, M. Allez, E. Sarfati and P. Valleur
Most patients retain their rectum but one-third have an ileostomy

460 **Treatment of advanced gastric cancer by palliative gastrectomy, cytoreductive therapy and postoperative intraperitoneal chemotherapy**
H. C. Jeung, S. Y. Rha, W. I. Jang, S. H. Noh and H. C. Chung
Tolerance is dependant on performance status

467 **Postoperative body-weight loss and survival after curative resection for gastric cancer**
W. Yu, B. Y. Seo and H. Y. Chung
Late weight loss suggests recurrence

471 **Impact of diagnostic laparoscopy on the management of gastric cancer: a prospective study of 120 consecutive patients with primary gastric adenocarcinoma**
T. Lehnert, B. Rudek, P. Kienle, K. Buhl and C. Herfarth
A case for selective laparoscopy

476 **Results of laparoscopic Nissen fundoplication at 2–8 years after surgery**
M. I. Booth, L. Jones, J. Stratford and T. C. B. Dehn
Longer-term results confirm efficacy

482 **Diethylmaleate, a pro-oxidant, attenuates experimental ischaemia–reperfusion-induced lung injury**
P. D. Kiely, J. C. Wang, C. J. Kelly, C. Condron, R. G. K. Watson and D. J. Bouchier-Hayes
Could prevent the inflammatory injury associated with reperfusion

486 **Risk of femoral hernia after inguinal herniorrhaphy**
T. Mikkelsen, M. Bay-Nielsen and H. Kehlet
Study from the Danish hernia database

489 **Correspondence**

502 **Book reviews**

506 **Scientific surgery**

507 **Vascular Surgical Society of Great Britain and Ireland abstracts**

527 **Instructions to authors**

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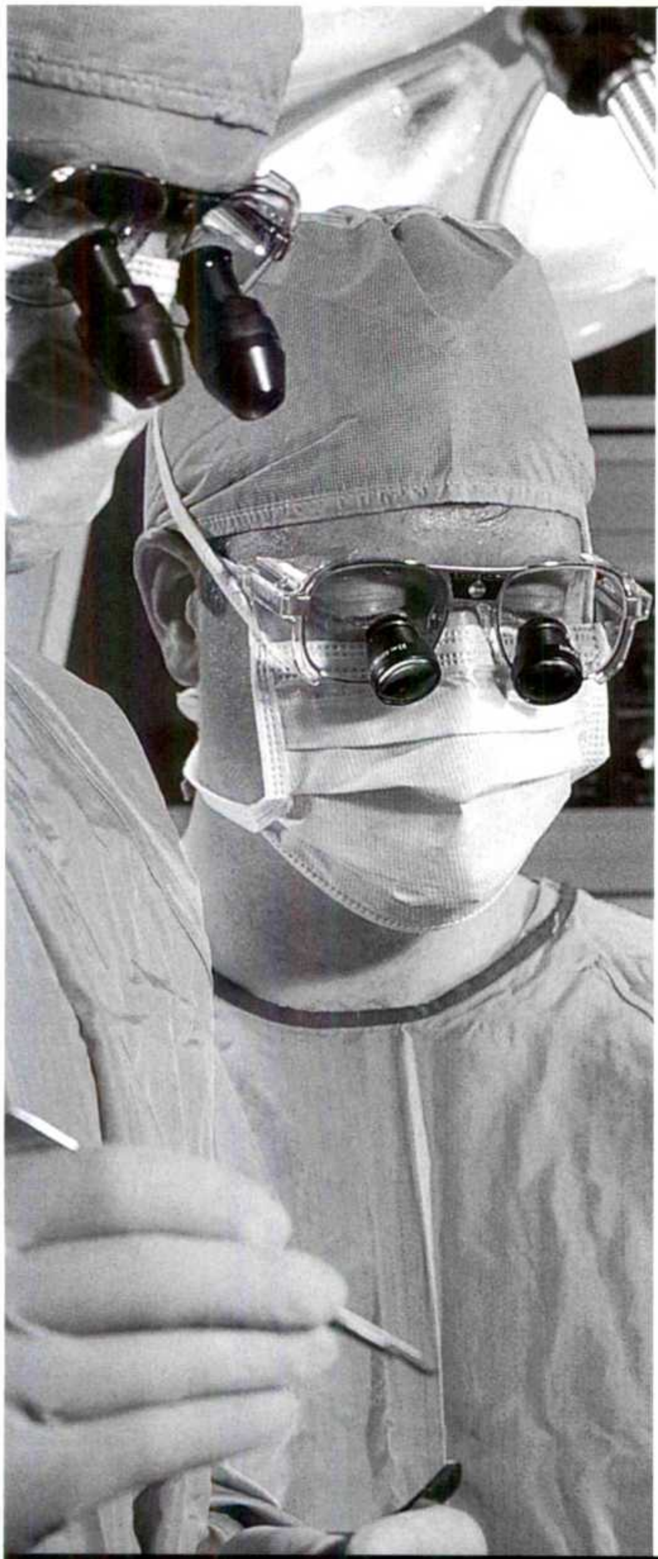

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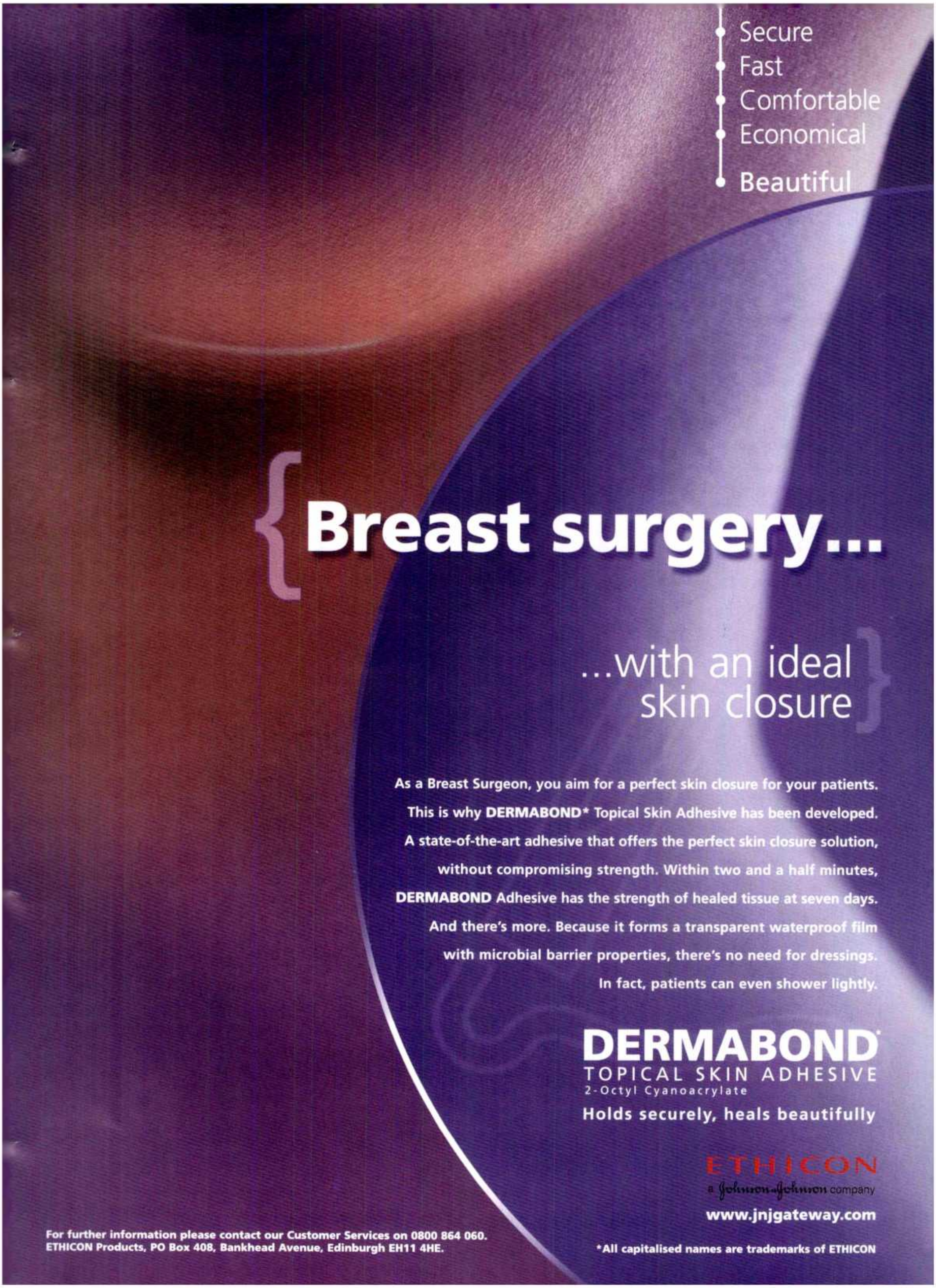

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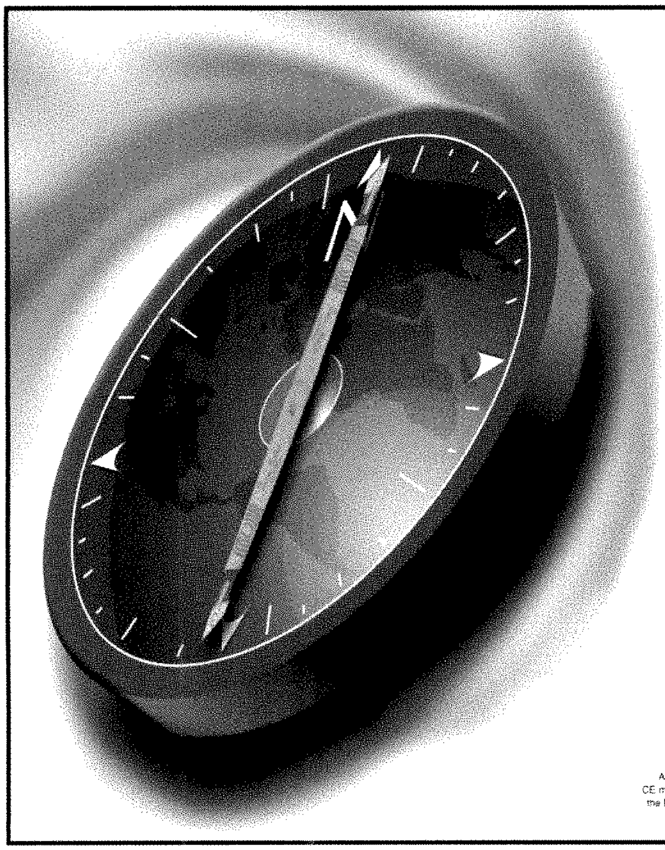

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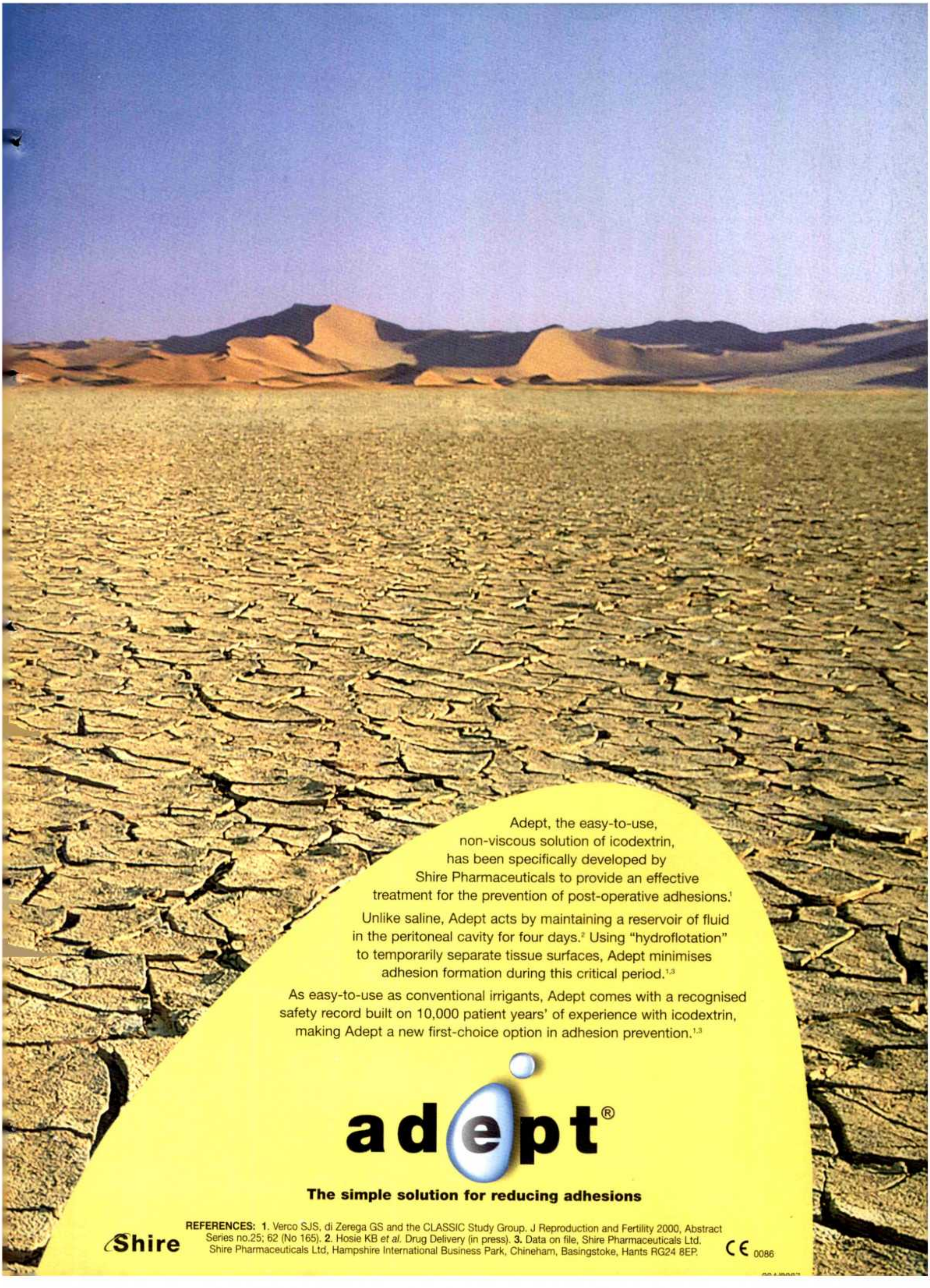

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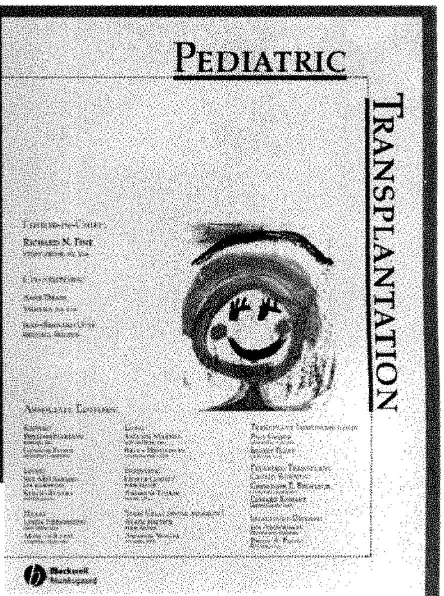

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Patients and surgeons expect a successful outcome from laparoscopic cholecystectomy for symptomatic gallbladder stones. The operation can be performed with a very short hospital stay, even as day-case surgery, and produces only minimal discomfort in most patients[1,2]. The occurrence of an accidental bile duct injury strikes the patient and surgeon with great force, as neither is prepared for this complication, which occurs in around 0·5 per cent of operations[1,3]. Often the surgeon is not immediately aware of this disaster, and a delayed diagnosis adds further difficulty to the potentially disturbed relationship between doctor and patient. Recognition of the injury, staging of its severity and further management are the surgical priorities; the literature on iatrogenic bile duct injury focuses on these topics and is very much oriented towards surgical management. The impact of this unexpected negative outcome on the patient's quality of life has hardly been given any attention, as demonstrated in a recent (October 2001) issue of the *World Journal of Surgery* dedicated to bile duct injury.

Articles on this subject can be divided into three types. First are papers that address the recognition and registration of injury. Many are audits and questionnaires on laparoscopic cholecystectomy, describing the incidence and mechanism of injury and various means of prevention[1,3,4]. Most papers address the so-called major injuries. Second are papers that address referral, and repair or reconstruction. These come from so-called specialist centres and report the severity of the injuries, their (mis)management in referral hospitals and the 'excellent' functional, usually short-term, outcome of repair[5–8]. There seems to be a high degree of professional satisfaction with the repair of another surgeon's problem, typified in statements such as 'a challenge for even the most skilled biliary tract surgeon'[5]. In these papers the 'minor' lesions are sometimes neglected, no doubt being regarded as less important (in particular for surgical heroism as they can be treated by non-surgical means). However, the only death in the present authors' series of 300 patients occurred after a 'minor' injury leading to biliary peritonitis and septicaemia. Third are the few papers that address malpractice, litigation and liability payment[9].

During follow-up of patients after repair of bile duct injury in this institution, a high prevalence of ill-defined abdominal complaints has been noticed; few of these patients had specific features such as jaundice or cholangitis. These vague symptoms contrasted with both the excellent functional outcome and the associated satisfaction of the surgeon after a sometimes difficult repair. In most of the patients the problems seemed to be associated with a belief that they had not been taken seriously at the time of the first postoperative symptoms; in the patients' opinion this had led to a delay in diagnosis of duct injury. They were disappointed by the reluctance of the primary surgeon to admit to procedural error and to give full information on the severity of the injury. Terms such as 'persistent leakage' and 'anatomical variation of the bile duct' were used, instead of 'leakage due to injury to the duct'.

This impression led the present authors to assess the quality of life as an outcome measure 5 years after repair of a bile duct injury sustained during laparoscopic cholecystectomy. The well validated Short Form 36 (SF-36) questionnaire was used. In all eight subscales, both physical and mental, quality of life was significantly impaired compared with that of control patients who had an uneventful laparoscopic cholecystectomy[10]. There was no difference between patients with minor or major injuries, or between those having endoscopic or open repair. However, duration of treatment was an independent prognostic factor, with prolonged treatment of even a so-called minor complication having great psychological impact.

These findings could be due partly to a selection bias caused by the referral pattern. They may also relate to the fact that only a few patients were involved in legal proceedings as malpractice litigation is uncommon in the Netherlands; it has been suggested by some that settlement and liability payment can lead to a reduction of complaints in these patients. The phenomenon of response shift bias may also be responsible for the poor quality of life as assessed by the SF-36 questionnaire, meaning that patients do not accept a reduction in daily health status after a surgical procedure that is perceived as relatively minor.

Until recently, studies from referral centres seem to have focused on outcome in terms of liver function test results and scintigraphy, rather than in terms of general well-being or quality of life. More work is needed to elucidate further this finding that quality of life is poor after an apparently successful repair of this serious complication of a common operation. The present authors' study[10] suggests that more careful and accurate communication between doctor and patient, before and after primary surgery as well as before and after repair surgery, may help to prevent such disappointing results.

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Leading article

Ecosurgery

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Earth's health is not at its best. Those of us who care (or should care) for the planet may not agree on a specific diagnosis but there is a general suspicion that 'progress' may be a fast growing and metastasizing cancer. As surgeons, we have a considerable responsibility in caring for our environment: first, as responsible citizens; second, as professionals taking care of the health of the population; and third, as users of knowledge, powerful technology and drugs to improve the length and the quality of life of our patients.

'Ecosurgery' may be regarded as a conceptual umbrella that translates the general principles of ecological thinking into practical issues for surgeons. It should be regarded as our contribution to our planet's well-being. This may seem arrogant, but in the following paragraphs I shall present some evidence indicating how surgeons can effectively contribute to saving valuable resources, reducing the amount of waste and helping to palliate pain and suffering.

1 More judicious hand scrubbing. Water is becoming a limited resource almost everywhere[1], a situation that will probably worsen in the future. A single 4-min scrub[2] with the tap left open consumes no less than 15–20 litres of water (A. Sitges-Serra, unpublished calculation). The reader can easily extrapolate the volume of water wasted during scrubbing for a whole surgical team and for the millions of operative procedures performed every day around the world. Furthermore, energy wastage is enormous if hot water is used. Hand or foot pedal-activated devices should be implemented in all scrubbing facilities to minimize water wastage. Research into waterless hand scrubbing should be encouraged[3], and brushless scrubbing should also be advocated as it appears to be just as safe as brush scrubbing while saving tons of plastic materials and paper envelopes[4].

2 Improving the use of antibiotics. While antibiotics are among the drugs most often used by surgeons, few of us realize how devastating they are from an ecological point of view. Even a single dose of a wide-spectrum antibiotic may induce massive changes in the resident intestinal flora[5]. Injudicious use of these drugs leads to increasing levels of bacterial resistance, more adverse drug reactions and an inevitable waste of money. Antibiotic prophylaxis in clean non-prosthetic surgery[6] is particularly relevant. Should we administer antibiotics to all patients undergoing clean surgery to spare a few (sometimes a very few) superficial wound infections? Even when treating established infections, surgeons should be aware that the therapeutic window for antibiotics is probably no longer than 72 h[7]. Serious questioning of all antibiotic treatments lasting over 5 days is needed, particularly in association with surgical procedures.

3 Alleviating suffering. Surgeons like aggressive and heroic surgery. However, hypercomplex operations have a very modest impact in terms of overall health and on the duration or quality of life of most individuals. Surgeons may even reduce the health of patients by submitting them to major procedures that result in severe postoperative complications, causing prolonged hospital stays and permanent organic or psychological damage[8]. Long and expensive operations, of uncertain outcome, are an issue of particular relevance for the elderly and the asymptomatic patient. As the goals of medicine change towards more effective palliation and symptom control[9], surgeons must become more aware of the wishes of our patients; the old Hippocratic dictum *primum non nocere* should not be forgotten.

4 Not using disposable materials if reusable ones are safe. It is astonishing to see the amount of 'surgical waste' produced, even by a medium-size operation: sponges, paper, gowns, masks, drapes, plastic gloves, disposable suturing devices, trocars and so on. In the era of recycling this is nonsense. There is no advantage, for example, in using disposable drapes and gowns; reusable textiles spare tons of paper-like materials. Choice of procedure is another concern. Why do some surgeons still insist on performing laparoscopic hernia repair when open surgery is both less expensive[10] and more 'ecological' as it produces less waste? Industrial research should be directed towards safer and more effective recycling of surgical and endoscopic instruments and of surgical waste.

5 Preferring a one-stage to a two-stage surgical procedure. One-stage procedures are to be preferred from most points of view: they are cost-effective, result in reduced hospital stay, require less drug administration, anaesthetic and operating time, cause less suffering, and are more likely to produce an early return to a normal life. As far as possible young surgeons should be trained to manage in one stage surgical conditions that have been traditionally handled in two stages, particularly colonic emergencies.

6 Better use of communication. In this first century of the new millenium, a time of impressively fast communication,

tremendous resources are still expended by industry and professional societies on medical and promotional meetings. Some reasons may be advanced in favour of travel to medical meetings, such as the management of professional politics and surgical societies, touristic incentives and gadget collection, but these offer little real benefit for patients. Reading the scientific surgical literature, liberal use of electronic mail and continuous education offered by selected websites can currently satisfy most of the needs of surgeons wishing to remain abreast of the advances in their specialty. The multiplication of medical meetings has no evidence-based benefit. Resources spent in such congresses might be more effectively employed in furthering more efficient communication systems, particularly for those many surgeons who cannot afford to travel to these 'vanity fairs'.

These are but a few examples of the lines along which ecosurgical thinking might develop. Keeping the best of our surgical tradition is not incompatible with the development of a new sensitivity towards ecological issues involving our profession.

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Review

Positron emission tomography for staging and management of malignant melanoma

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Background: The incidence of malignant melanoma is rising; it now has an incidence of ten per 100 000 per annum in the UK. The development of metastases is unpredictable, but prognosis is linked directly to the initial stage at diagnosis. Positron emission tomography (PET) can allow the detection of malignant cells at a relatively early stage.

Methods: A review of the literature was undertaken by searching the Medline database for the period 1980–2000 without any language restrictions.

Results: The overall sensitivity and specificity of PET are 74–100 and 67–100 per cent respectively. PET has a reduced sensitivity and specificity for thinner lesions (less than 1·5 mm). Comparison with computed tomography and magnetic resonance imaging has shown a higher sensitivity and specificity for PET in all regions of the body except the thorax.

Conclusion: Currently the accepted indication for PET is recurrent melanoma when surgical intervention is being considered. However, other potential indications include the detection of occult or distant metastasis at initial presentation and the clarification of abnormal radiological findings at follow-up. The routine use of PET for American Joint Commission on Cancer stage I or II disease is of uncertain benefit and is not indicated at present.

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Introduction

The incidence of malignant melanoma has been rising steadily over recent decades[1–4]; UK data indicate an incidence of ten per 100 000 per annum, with a lifetime risk of one in 200[5]. The development of metastases from melanoma is unpredictable in individual patients[6,7] but prognosis is linked directly to initial stage at diagnosis. To implement appropriate management and improve the prognosis, accurate staging is essential. The 5-year survival rate for stage I disease is 80 per cent, and for stage II disease 36 per cent. Stage IV disease is generally incurable and is associated with a median survival of 6 months[8,9].

The current treatment for malignant melanoma is surgical excision with intention to cure. Adjuvant treatment modalities have met with limited success. There is a significant incidence of systemic relapse after radical surgery within 5 years for both stage I and stage II melanoma[10,11], and systemic disease is inevitable after resection of local or regional metastases[12]. These features suggest that occult metastases are common at the time of initial diagnosis. Established diagnostic procedures for initial staging include physical examination, chest radiography, ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) and lymphoscintigraphy[13–16]. However, these modalities have met with limited success in the detection of small metastases. The introduction of positron emission tomography (PET) is aimed at detecting micrometastases based on abnormal cellular metabolic activity, rather than relying on structural changes; PET may be able to detect metastatic disease earlier than conventional investigation.

PET is a non-invasive, high-resolution, imaging modality. Di Chiro *et al.*[17], in the 1980s, initially used the technique as a research tool to characterize brain tumours. Although PET is not in general clinical use, it has gained increasing acceptance in oncology because malignant cells have a higher rate of utilization of glucose than normal cells[18]. PET scanners have been developed that are capable of acquiring whole-body images in a short timeframe, combined with full three-dimensional image reconstruction. Positron-emitting radiopharmaceuticals can be used to target malignancy at an early stage.

Methods

A review of the literature was undertaken by searching the Medline database for the period 1980–2000 without any language restrictions. Keywords included 'PET scanning', '^{18}FDG', 'melanoma – staging/treatment' and 'sentinel node biopsy'. All articles were checked manually and included only if they were both relevant and contained new information. Unpublished data and conference proceedings were not included.

Principles of positron emission tomography

The commonest application of PET in oncology is based on the finding of Warburg[18] in the 1930s that malignant cells exhibit enhanced glycolysis. Viable and rapidly dividing tumour cells have a greater rate of glucose utilization than normal tissues. While this is thought to be due primarily to an increased number of glucose membrane transporters, it has also been shown that there is an increase in intracellular hexokinase, phosphofructokinase and pyruvate dehydrogenase activity[18,19]. The increased utilization of glucose in malignant cells is associated with an accumulation of 2-deoxyglucose, a molecule that is structurally similar to glucose. In the cell, 2-deoxyglucose is phosphorylated and cannot be further metabolized, except by further limited dephosphorylation, and as a result becomes trapped[20]. When labelled with ^{18}F, 2-deoxyglucose has been shown to accumulate in human tumours to such an extent as to allow imaging[21].

Glucose is thought to accumulate in malignant cells as a result of the upregulation of glucose transport molecules on the cell surface. Activation of *GLUT1*, a gene that codes for the synthesis of glucose transporters, is thought to be an early marker of malignancy[21]. As a result of the increased expression of *GLUT1*, [^{18}F]fluorodeoxyglucose (^{18}F-FDG) shows increased movement into malignant cells compared to its progress into normal cells. However, ^{18}F-FDG is a non-specific metabolic agent that reflects increased glucose metabolism and increased anaerobic glycolysis regardless of the underlying cause. It can therefore be concentrated in any cell with increased glucose utilization[22] or tissue oxygenation, or when there is increased regional blood flow or an inflammatory reaction[23]. These features are responsible for a decreased specificity of ^{18}F-FDG for recognition of malignant cells.

As ^{18}F-FDG decays it emits a positron, which in turn collides with a negatively charged electron. The two particles annihilate each other, leading to the formation of two photons, each with energy of 511 KeV, which are emitted at 180° to one another[24]. The PET scanner is designed to detect these photons and determine their point of origin in order to produce an image based on the detected activity. Within the past 5 years there has been a significant improvement in both the hardware and, particularly, the software required for this type of scanning. This has resulted in an increased utility and acceptance of the technique. The 'gold standard' remains full-ring, multi-crystal, whole-body tomography, which makes use of bismuth germanate oxide radiation detectors and detector assemblies[25,26]. However, to be competitive with other imaging modalities, new radiation detector technology is being developed (e.g. lutecium orthoillicate), and the basic Anger γ camera with sodium iodide crystals has been adapted such that PET can be performed. The role of these newer detectors has yet to be defined, and their sensitivity and specificity assessed.

A significant difficulty when comparing the results of PET from different centres is that no universally accepted standard has been adopted for its use. Protocols differ from centre to centre, although the following procedures are generally adopted. (1) Patients are fasted before scanning to maximize glucose uptake into malignant cells and to decrease normal myocardial glucose uptake[22]. (2) Blood glucose levels are checked before scanning. (3) Hyoscine butylbromide may be administered to reduce uptake in the bowel, which may lessen the accuracy of the scan. (4) Exercise is avoided before the scan to prevent increased glucose uptake into muscles. (5) Scans are usually obtained from the base of the skull to the upper third of the legs; in some centres whole-body scans can be acquired.

Whole-body data can be analysed either in terms of the qualitative pattern of distribution of the radiolabelled tracer or by the quantitative measurement of tracer uptake at a specific site. Normal significant uptake is always noted in the brain and myocardium. The stomach, liver, spleen, muscles and the lumen of the gastrointestinal tract all take up ^{18}F-FDG to a variable degree. ^{18}F-FDG tracer is excreted via the kidneys and so these, along with the ureters, bladder and urethra, also demonstrate increased uptake. Quantification of FDG uptake may be useful for differentiating benign from malignant tissue and in determining the treatment response of malignant cells[27–32]. The standardized uptake value (SUV) has been proposed as a simple index of tissue and tumour accumulation that is independent of patient size[33]. SUV has been defined as tissue concentration (kilobecquerels per millilitre) divided by activity injected per body-weight (kilobecquerels per gram). The SUV is also known as the differential absorption ratio[29] and the differential uptake ratio[32].

Table 1 Overall sensitivity and specificity of positron emission tomography in the detection of metastatic disease from malignant melanoma

Reference	Year	No. of patients	Sensitivity (%)	Specificity (%)
Gritters *et al.*[34]	1993	12	92	100
Steinert *et al.*[35]	1995	33	92	77
Boni *et al.*[36]	1995	15	91	67
Blessing *et al.*[37]	1995	20	74	93
Damian *et al.*[38]	1996	100	93	—
Wagner *et al.*[39]	1997	11	100	100
Rinne *et al.*[40]	1998	100	91	94
Holder *et al.*[41]	1998	76	94	83
Macfarlane *et al.*[42]	1998	23	85	91
Acland *et al.*[43]	1999	54	87	78

Table 2 Classification of malignant melanoma

	MD Anderson classification	AJCC staging
Primary malignant melanoma thickness (mm)		
< 0·75	I	Ia
0·76–1·49		Ib
1·5–4·00		IIa
> 4·00		IIb
Localized spread		
Local recurrence satellite	II	
Regional spread		
In-transit metastasis	IIIa	III
Regional lymph node metastasis	IIIb	
Distant spread		
Distant metastasis	IV	IV

AJCC, American Joint Commission on Cancer

Table 3 Sensitivity and specificity of positron emission tomography in the different stages of malignant melanoma (after Acland *et al.*[43])

Stage	Sensitivity (%)	Specificity (%)
I	50	87
II	33	100
III	93	50
IV	Not assessed	Not assessed

Sensitivity and specificity of positron emission tomography

The major benefit of using PET for malignant melanoma is the detection of metastatic disease at a potentially curable stage. The earlier the melanoma is detected, the more effective the potential options are likely to be. In view of this, several trials have examined not only the overall sensitivity and specificity of PET but also its effectiveness at each clinical stage of melanoma. A subgroup of trials has also assessed the sensitivity and specificity of PET in the regional staging of melanoma.

Overall sensitivity and specificity

PET has an overall sensitivity of 74–100 per cent and a specificity of 67–100 per cent (*Table 1*). Gritters *et al.*[34] carried out the initial study of PET in 12 patients with histologically proven malignant melanoma in the early 1990s. Imaging by CT and PET was focused on the areas of suspected metastatic disease. Although the value of the study was somewhat limited by the small number of patients and lack of whole-body scanning, it showed a sensitivity of 92 per cent and a specificity of 100 per cent for PET when compared with CT. These values have since been corroborated by further, larger trials[34–38, 40,41, 43]. Damian *et al.*[38], in 1996, investigated prospectively 100 patients with varying stages of malignant melanoma and compared the sensitivity of PET to that of conventional imaging. This study showed an overall sensitivity of 93 per cent for PET. Rinne *et al.*[40] also carried out a prospective trial of 100 patients with 'high risk' melanoma (thickness greater than 1·5 mm). Using both conventional diagnostic methods (excluding sentinel lymph node imaging) and PET, they tried to establish the presence of metastatic disease. PET had an overall sensitivity of 91 per cent and a specificity of 94 per cent, compared with 57 and 45 per cent, respectively, for CT.

Sensitivity and specificity with respect to clinical stages of melanoma

In the trials that were reviewed, the most commonly used classification of malignant melanoma was the MD Anderson classification. However, the American Joint Commission on Cancer (AJCC) staging (*Table 2*) was also used in some instances.

Stage I and II disease

Acland *et al.*[43] assessed the sensitivity and specificity of PET for each of the stages of malignant melanoma (*Table 3*). This was a retrospective study of the 54 patients who presented to their institutions (Guy's and St Thomas's Hospital, London, UK) with a histological diagnosis. The MD Anderson classification was used to stage the patients at original presentation. The overall sensitivity and specificity were 87 and 78 per cent respectively, and so were broadly similar to those of other studies[34,38,40]. However, all patients with stage I disease were included and follow-up was longer (36 months) than in most trials, which might have increased the false-negative rates. For stage I disease PET had an overall sensitivity of 50 per cent. However, of the four false-positive results, three were in patients with melanomas of less than 1·5 mm in thickness. This suggests that PET may be of limited value in stage I disease, especially in the case of thinner lesions. Specificity for stage I disease was 87 per cent.

The finding that PET has reduced sensitivity in the identification of thinner primary lesions is supported by a number of other trials[38,44,45]. Damian *et al.*[38], although showing an overall sensitivity of 93 per cent, reported 16 lesions that were not demonstrated by PET. Of these, 15 were less than 1 cm thick. Paquet *et al.*[44] also demonstrated an increased number of false-negative PET scans when the tumour size was less than the spatial resolution of the scanner (e.g. less than 0·5–1·0 cm). Tyler *et al.*[45] also showed the limitations of PET at the present time. First, of 11 scans that were negative in clinically evident melanoma, only two of the foci were greater than 1 cm in diameter. Second, a number of clinically negative nodal basins was cleared in the study to facilitate hyperthermic isolated limb perfusion. In this group ten patients had microscopic foci of melanoma present pathologically that were not detected by PET.

PET in stage II melanoma was found by Acland *et al.*[43] to have a sensitivity of 33 per cent and a specificity of 100 per cent. The low sensitivity was attributed to the small number of patients within this staging classification. Still, it is clear from these results, however limited, that the role of PET in stage I or II melanoma (MD Anderson classification) is very uncertain. Further trials will be needed if PET is to be shown to be of benefit in the earlier stages of malignant melanoma.

Stage III disease

Acland *et al.*[43] demonstrated a 93 per cent sensitivity and a 50 per cent specificity in stage III malignant melanoma. This result correlates well with a trial conducted by Tyler *et al.*[45], a prospective study of 95 patients with clinically proven stage III disease (AJCC staging) which showed a sensitivity of 87 per cent and a specificity of 44 per cent. The specificity was low because of an inability to confirm PET-positive areas with histological findings. However, these two trials emphasize the benefit of PET in the diagnosis of metastatic disease when the initial melanoma is more than 1·5 mm thick.

Three trials have demonstrated an alteration in clinical management after the use of PET to assess the presence of metastatic disease. Damian *et al.*[38] described an alteration in the management of 22 of 100 patients by determining their suitability for surgical resection. PET identified 'unsuitable candidates' by uncovering previously unsuspected widespread metastatic disease, and identified 'suitable candidates' by confirming the presence of only local metastatic disease. Acland *et al.*[43] also demonstrated upstaging in 28 per cent of their patients with stage III melanoma to stage IV melanoma, which significantly altered their management. Tyler *et al.*[45] also upstaged 16 per cent of their patients as a result of PET.

Regional sensitivity and specificity

Trials[36,40,43] have shown that PET is superior to conventional imaging such as CT and MRI in the detection of regional and mediastinal lymph nodes, liver and soft tissue metastasis. Rinne *et al.*[40] demonstrated this by a direct comparison between the sensitivities and specificities of PET and CT in various regions of the body (*Table 4*). Blessing *et al.*[37] compared PET and ultrasonography in the detection of regional lymph nodes. Their results indicated that both imaging modalities had similar sensitivities and specificities: 74 and 93 per cent for PET and 76 and 93 per cent for ultrasonography respectively.

In contrast to these results PET has been shown to be less sensitive than other imaging modalities for pulmonary metastasis. This was first reported by Gritters *et al.*[34], who noted that the only area in which PET had a lower

Table 4 Sensitivity and specificity of positron emission tomography and computed tomography in the detection of metastatic disease (after Rinne *et al.*[40])

	Positron emission tomography		Computed tomography	
Region	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Mediastinum/hilum	71	100	20	87
Abdomen	100	94	27	78
Abdominal lymph node	100	100	83	100
Peripheral lymph node	97	100	51	92
Lung	70	100	87	100

sensitivity than CT was in the detection of lesions in the lung. This is consistent with the findings of Rinne *et al.*[40], who demonstrated that PET had a lower sensitivity than conventional imaging in the detection of pulmonary metastatic disease (70 per cent for PET *versus* 87 per cent for conventional imaging). These lower rates have been attributed to either blurring caused by respiratory movement or a limited resolution of PET due to the low density of lung tissue and increased positron range.

Application of positron emission tomography in the staging and management of melanoma

Elective resection of the primary site of malignant melanoma with intention to cure is the aim of treatment. However, the decision to perform elective lymph node dissection of clinically uninvolved regional lymph nodes on the basis of the suspicion of micrometastases is controversial. Lymph node dissection has a complication rate of 5–40 per cent, depending on the operative technique, the extent of dissection and the site of disease[46]. Ideally nodal dissection should be considered only in patients with proven metastatic lymph node involvement.

The initial study by Gritters *et al.*[34] assessed the accuracy of PET in the identification of regional lymph node status. In this study metastatic disease was identified correctly in seven of seven tumour-involved nodal groups, including foci detected within three lymph node groups that were considered normal by clinical and CT criteria. PET also correctly identified the lack of tumour involvement in six of six lymph node regions, including two enlarged nodes for which pathological confirmation was obtained. A prospective trial by Macfarlane *et al.*[42] of 22 patients with a primary lesion less than 1·5 mm thick concurs with these findings. Both elective and therapeutic lymph node dissections were included. The overall sensitivity and specificity were 85 and 92 per cent respectively. Regional lymph node status was predicted accurately in 88 per cent of cutaneous malignant melanoma cases. However, this study had one false-positive and two false-negative results. The false-positive was due to a reactive lymph node after biopsy, and one of the false negatives had only seven malignant cells in a marginal node sinus. Therefore, although the study demonstrated a high positive predictive value, a negative finding does not completely rule out the presence of metastatic disease.

Wagner *et al.*[47] did not corroborate these results. They studied 70 patients with AJCC stage I, II or III disease prospectively to compare the sensitivity and specificity of PET with those of sentinel node biopsy in the detection of regional lymph node metastasis. One of the most useful methods for staging malignant melanoma is surgical evaluation of the regional lymph nodes.

Table 5 Sensitivity and specificity of positron emission tomography and sentinel node biopsy (after Wagner *et al.*[47])

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PET	17	96	50	82
Biopsy	94	100	100	99

PET, positron emission tomography; PPV, positive predictive value; NPV, negative predictive value

Morton *et al.*[48] and other investigators[49–51] have recently developed technology to biopsy the sentinel lymph node. The histological status of the lymph node has been shown to be an important prognostic factor in melanoma[52,53]. Lymphatic mapping with sentinel node biopsy reliably identifies patients with occult regional nodal metastatic disease. It has a high accuracy and a low morbidity rate, and has the ability to select patients for lymphadenectomy or adjuvant immunotherapy. However, it should be noted that sentinel node biopsy has no role in the detection of distant metastatic disease. The value of PET depends on its ability to detect small tumour burdens in the regional lymph nodes and distant organs. The trial by Wagner *et al.*[47] showed that PET was insensitive in the detection of occult nodal metastatic disease demonstrated by sentinel node biopsy (*Table 5*). This was thought to be due to the minimal tumour volumes involved, but there were no data to prove that PET was insensitive in the detection of distant sites of metastasis.

Limitations of positron emission tomography

A review of the literature suggests that PET and conventional imaging should be regarded as complementary rather than competing imaging modalities. Blessing *et al.*[37] showed that although the sensitivity and specificity of ultrasonography and PET were similar for regional lymph node analysis ultrasonography was more practical. Not only was it easier to perform, it was also less time consuming and less expensive than PET. However, ultrasonography has the disadvantage of requiring all the lymph node basins to be examined individually. Although trials have shown that PET has a greater overall sensitivity and specificity than CT[40,41], the main disadvantage here lies in the fact the PET provides less accurate anatomical localization of metastatic disease and so typically requires follow-up with conventional imaging.

Although PET is an expensive imaging technique, it is increasingly being advocated as cost-effective. The initial cost of establishing a scanner accounts for the majority of the expense; whole-body PET scanning is still cheaper than whole-body MRI[54,55]. A study by Valk *et al.*[56] has shown that PET is cost-effective in stage II and III malignant melanoma, with a savings : cost ratio of 2 : 1 when used as an additional procedure, and of 4 : 1 should CT of the chest and abdomen be eliminated. However, the cost-effectiveness of PET in stage I melanoma is more difficult to ascertain.

The role of PET in current clinical practice for patients with localized melanoma remains uncertain. Although past trials have demonstrated the overall sensitivity and specificity of PET, they are of limited value because they compare PET to clinical examination or current imaging modalities, both of which have been shown to be inaccurate in the diagnosis of occult malignancy. There are no proven data to demonstrate definitively the benefit of PET in the detection of micrometastatic disease at the original presentation of the patient. Furthermore, evidence on the value of PET in the determination of occult disease in the regional lymph node basins is incomplete, although this is of less importance because of the use of sentinel lymph node biopsy. While PET compares favourably with conventional imaging of regional lymph nodes, it is less sensitive than the evolving sentinel node biopsy technique.

Further limitations of PET include its inability to recognize tumour specifically. In the case of malignant melanoma, animal studies of human tumour xenografts have shown that these cells exhibit one of the highest neoplastic uptakes and tumour : blood ratios[57]. However, FDG also accumulates in non-neoplastic tissues, especially those involved in infection and inflammation[58,59]. Inflammation after operation or radiotherapy is particularly relevant. On the positive side, however, it is thought that malignant cells have a greater and more intense uptake of FDG than those involved in infectious processes[60]. A final difficulty involves the normal uptake of FDG into metabolically active tissues, such as brain and myocardium, leading to uncertainty in the interpretation of scans in these areas.

Conclusion

PET provides a non-invasive imaging tool for the assessment of malignant melanoma. Its value lies in its ability to visualize high metabolic activity, particularly in rapidly dividing tumour cells, thereby allowing the early diagnosis of metastatic disease. The sensitivity of PET in detecting metastatic disease is reduced with decreasing tumour size. When the original tumour is thin, the sensitivity of the technique is low relative to its overall sensitivity. PET is most valuable in stage III disease, where it may alter clinical management.

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Review

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Acute compartment syndromes

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Background: Acute compartment syndrome is both a limb- and life-threatening emergency that requires prompt treatment. To avoid a delay in diagnosis requires vigilance and, if necessary, intracompartmental pressure measurement. This review encompasses both limb and abdominal compartment syndrome, including aetiology, diagnosis, treatment and outcome.

Methods: A Pubmed and Cochrane database search was performed. Other articles were cross-referenced.

Results and conclusion: Diagnosis of limb compartment syndrome is based on clinical vigilance and repeated examination. Many techniques exist for tissue pressure measurement but they are indicated only in doubtful cases, the unconscious or obtunded patient, and children. However, monitoring of pressure has no harmful effect and may allow early fasciotomy, although the intracompartmental pressure threshold for such an undertaking is still unclear. Abdominal compartment syndrome requires measurement of intra-abdominal pressure because clinical diagnosis is difficult. Treatment is by abdominal decompression and secondary closure. Both types of compartment syndrome require prompt treatment to avoid significant sequelae.

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Introduction

Acute limb compartment syndrome (LCS) is a condition in which raised pressure within a closed fascial space reduces capillary perfusion below a level necessary for tissue viability[1]. This condition has been recognized since 1881 when Volkmann first described the contracture that is a common sequela[2]. The first reported treatment of LCS was by Petersen in 1888[3]; Jepson was the first author to demonstrate it experimentally in 1926[4]. LCS is sometimes confused with the crush syndrome; however, the former refers to local manifestations and sequelae of increased pressure whereas the latter, though part of the same spectrum of disease, refers to systemic manifestations that include acidosis, hyperkalaemia, myoglobinuria, shock and acute renal failure[5].

Abdominal compartment syndrome (ACS) is a pattern of altered cardiovascular haemodynamics, respiratory mechanics and renal function occurring secondary to a sustained increase in intra-abdominal pressure (IAP)[6]. ACS was first suggested as an entity by Baggot in 1951[7], although the concept has only become widely accepted in the past 20 years. In this review the aetiology, clinical features, diagnosis and treatment of both acute LCS and ACS are discussed.

Methods

A Pubmed and Cochrane database search was performed with the key words acute, abdominal, vascular, orthopaedic, compartment and syndrome. All abstracts were reviewed and all articles in which more than three cases of compartment syndrome could be identified were further scrutinized. Further references were extracted by cross-referencing.

Limb compartment syndrome

Pathophysiology

The initial injury, whether traumatic or haemorrhagic, leads to swelling within a compartment. This causes an increase in intracompartmental pressure (ICP) with compressive closure of the thin-walled venules resulting in hypertension at the venous end of the capillary beds[8]. A rise in the hydrostatic force results in a further increase in ICP thus developing a vicious cycle[8]. Eventually arteriolar compression occurs, leading to muscle and nerve ischaemia with muscle infarction and nerve damage if prompt treatment is not instituted[9]. Other causes for the increase in ICP are external compression, postischaemic reperfusion injury and a decrease in the size of the compartment[10]. In ischaemia–reperfusion injury polymorphonuclear leucocytes, free radicals and other factors, such as tumour necrosis factor and leukotrienes, are thought to be responsible for a complex mechanism leading to the leakage of fluid from the intravascular compartment leading to the compartment syndrome[11,12].

Pathology

Hoffmeyer and co-workers[13] compared the histological findings in muscles of patients with acute early and late presentation of LCS. In the early stage of this syndrome they found marked perifascicular and intrafascicular oedema with dissociation of the muscle fibres and necrosis. In the late stages marked atrophy and hypertrophy of muscle fibres containing numerous lipid globules aligned in the intermyofibrillar spaces were found.

Aetiology

LCS may be classified as orthopaedic, vascular, iatrogenic or soft tissue injury on the basis of its aetiology (*Table 1*). It is important to emphasize that this division is only a simplification and in most cases a combination of factors is causative.

Orthopaedic

The commonest fractures implicated in LCS are those of the tibial shaft[3,14–19] and the distal radius and ulna[18,20–22]. The incidence after closed tibial fractures in different series ranges from 1·5 to 29 per cent[17,23–27] while in open fractures of the tibia it is between 1·2 and 10·2 per cent[14,17,19]. The incidence varies significantly between institutions because of the various techniques for measuring ICP and the different thresholds for performing fasciotomy. There is no difference in ICP between open and closed fractures, so it is important to remember that open fractures are as likely to develop LCS and require treatment as closed[23,25]. In the leg the anterior compartment is most commonly affected whereas in the forearm it is the flexor compartment[17,28].

Table 1 Common causes of acute compartment syndrome

Limb	
Orthopaedic	Tibial fracture Forearm fracture
Vascular	Ischaemia–reperfusion injury Haemorrhage Phlegmasia caerulea dolens
Iatrogenic	Vascular puncture in anticoagulated patients/ haemophiliacs Intravenous/intra-arterial drug injection
Soft tissue injury	Prolonged limb compression Crush injury Burns
Abdominal	
Trauma	Blunt Penetrating
Haemorrhage	After surgery Ruptured abdominal aortic aneurysm

Comminuted fractures are more prone to compartment syndrome and this may reflect the high energy required to cause this type of fracture[14]. LCS has also been described in femoral and calcaneal fractures[29–31]. Femoral fractures, however, have a lesser association with LCS because the surrounding fascial compartments are large and, furthermore, communicate with the muscles of the hip allowing extravasation of blood outside the compartmental envelope[29]. In children, crush injuries to the foot with concurrent fractures may lead to the development of foot compartment syndrome[32].

Closed therapeutic interventions for these fractures are liable to increase ICP and lead to a compartment syndrome. These include traction[33], cotton padding and plaster cast[10], and manipulation of bones[26,34]. Following splitting and loosening of a plaster cast there is a reduction in ICP, but the pressure again rises after reduction[34]. Operative treatment of fractures with intramedullary nailing can also lead to the LCS[18,23,30,35]. The incidence in different series ranges from 0 to 7 per cent[24,26,35,36]. Intramedullary nailing increases ICP maximally peroperatively, with a subsequent decrease over the following 15 min to 36 h[23,26].

Anticoagulation with warfarin or heparin after operation to replace a joint has led to compartment syndrome[37]. The symptoms in this situation may mimic common postoperative pain thereby leading to delay in diagnosis. Cases have also been described after the use of a pulsatile irrigation system for wound irrigation[38].

Vascular

Vascular causation leading to compartment syndrome includes both arterial and venous injury[30,39–41]. It also includes traumatic arterial injury which in combination with vein trauma is more likely to require a fasciotomy[42]. Injury to the popliteal vessels, particularly when there is a concomitant fracture, is most likely to result in LCS[39,43–47]. In the thigh, vascular injury may result in localized compartment syndrome without distal circulatory compromise[30].

Any procedure that revascularizes the leg, such as embolectomy, thrombolysis and bypass surgery, can result in LCS, which is also known as postischaemic compartment syndrome and is due to tissue swelling following reperfusion[41,48–51]. The incidence of LCS after revascularization ranges from 0 to 21 per cent[39,49,50–57]. Risk factors identified for development of the syndrome in this context are prolonged ischaemic time, acute onset of ischaemia, increasing age, decreased arterial pressure, inadequate backflow during the revascularization procedures, need for a distal procedure after proximal reconstruction, intraoperative shock and vein harvest in the same limb[52,53].

One of the signs of LCS after revascularization is a 'woody hard' swelling of the limb. Some authors have suggested that this limb swelling is predominantly due to subcutaneous oedema rather than increased ICP[57,58]. Qvarfordt and co-workers[59], however, have shown that following revascularization ICP rises with a maximal increase on the sixth or seventh postoperative day. Scott *et al.*[58] also noted that ICP increased from the third day after bypass surgery to a maximum on both the third and fifth day, although continuous pressure monitoring after revascularization did not alter the management of their patients. A combination of revascularization and deep vein thrombosis may be a further risk factor for the disease[59,60].

Other uncommon causes of vascular compartment syndrome include intra-aortic balloon pumping, isolated limb perfusion and phlegmasia caerulea dolens. Intra-aortic balloon pumping is used as a mechanical circulatory support for patients with severe ischaemic heart disease. This technique instruments the femoral artery and has led to compartment syndrome in 6–19 per cent of patients, presumably as a result of compromise to lower limb perfusion when the device is in place followed by reperfusion injury when it is removed[61,62]. Isolated limb perfusion is used mainly for chemotherapy and can lead to limb toxicity which may manifest as compartment syndrome or rhabdomyolysis[63]. Phlegmasia caerulea dolens occurs when an iliofemoral thrombosis extends to the venular and capillary levels, leading to venous gangrene[64–67]. When this occurs, there is commonly an underlying malignancy or other hypercoagulable state[68,69]. In patients with ACS, the raised IAP can lead to venous stasis which can in turn cause a LCS[10].

Iatrogenic

Iatrogenic causes of compartment syndrome include intravenous or intra-arterial injection and venous or arterial puncture in anticoagulated patients[70,71]. Intravenous administration of drugs has led to both forearm and hand compartment syndromes[70]. Pneumatic antishock garments and military antishock trousers (MAST) used for abdominal or pelvic haemorrhage may also lead to compartment syndrome[72,73]. The LCS in this situation is more likely to be bilateral[73] and it is therefore suggested that MAST should only be used where the hypotension is due to external blood loss. This is because of the increased risk of developing LCS in hypotensive patients as explained below. It is also due to the additive effect of the externally applied pressure to that already existing within a compartment[28,74]. In some haemophiliacs, compartment syndrome has developed spontaneously without any known trauma[75].

Soft tissue injury

Soft tissue swelling without a fracture may occur following a direct blow to a muscle compartment or after a crushing injury, particularly in patients with a bleeding diathesis[18,30,76]. In contusion injury continued use of the involved muscle groups may further increase ICP and increase bleeding leading to LCS[76]. Even minor injury, such an ankle sprain, may result in LCS[77]. In obtunded patients after drug or alcohol overdosage, prolonged limb compression may lead to soft tissue injury and LCS[5,9,20,78–80]. Burns have also been noted to cause both LCS[81] and ACS. Recognition of the syndrome in burn patients is difficult owing to concurrent soft tissue injury. Prolonged surgery is also a rare but preventable cause of LCS; it is especially prevalent in the Lloyd-Davies or Trendelenburg positions[82–84]. ICP increases with the time spent on the operating table and is further related to the position of the patient[85,86].

Intravascular drug abuse

Drug addicts who have injected toxic substances such as heroin, morphine, lysergic acid diethylamide and methadone into an artery have developed LCS[78,79]. Addicts may also suffer acute non-traumatic rhabdomyolysis leading to the syndrome[87].

Systemic hypotension

LCS is increased in the presence of systemic hypotension because of the lower ICP needed to compress vessels and so reduce tissue perfusion[8,30,73]. This has been demonstrated in a canine model in which significant muscle damage was demonstrated with an ICP of 20 mmHg for 6 h (mean arterial pressure 65 mmHg); ICP was 40–50 mmHg in the normotensive state[88].

Symptoms and signs (*Table 2*)

The symptoms of compartment syndrome are pain (usually out of proportion to the apparent injury) and paraesthesia. The consistent clinical signs are tense, swollen compartments, pain on passive stretching of the muscle and sensory loss. Pulselessness is not common or noted only at a late stage; it implies a vascular injury[3]. The loss of two-point discrimination is a sensitive sign in differentiating compartment syndrome from raised ICP alone[20]. The distribution of sensory changes can help in differentiating which compartments are affected[3] but all of these signs can be

Table 2 Symptoms and signs of acute compartment syndrome

- Limb
  - Pain (severe and out of proportion to the apparent injury)[3,8,22,89]
  - Pain on passive movement[3,9,20,22,79]
  - Swollen and tense compartment[20,29,70,79,89,90]
  - Progression of the above over a short time period
  - Paraesthesia (especially loss of two-point discrimination)[3,8,79,89,90]
  - Pallor and pulselessness (usually with a vascular injury)[20,90]
  - Paralysis (late symptom)
- Abdominal
  - Tense abdomen
  - Cardiorespiratory compromise
  - Oliguria/anuria

recognized only in the fully conscious patient[70]. The traditional symptoms and signs of pain, paraesthesia, pallor, pulselessness and paralysis are usually evident after vascular injury. In patients with arterial puncture injury, ecchymosis and swelling may also occur[71,91].

Measuring intracompartmental pressure

ICP measurement should be undertaken in unconscious patients and those whose conscious level is impaired. It is also useful in young children and in patients with regional nerve blocks, and when the clinical symptoms and signs are equivocal. It is not necessary if the diagnosis is clinically evident[8]. No studies are available that directly compare progression in the severity of clinical signs with direct ICP measurement. However, continuous monitoring can alter management and allow early fasciotomy, thereby avoiding possible sequelae[17,33]. It should be noted that many hospitals in the UK do not have equipment for the measurement of ICP[92]. Clinical assessment of ICP must be repeated, preferably by the same clinician, at frequent intervals (30 min to 2 h) to detect a progressive compartment syndrome. Many methods have been used clinically for the measurement of ICP and those commonly used are described below, along with their advantages and disadvantages.

Wick catheter

The original wick catheter technique was modified by Mubarak and co-workers[9,93] who used polyglycolic acid suture wicks connected to a pressure transducer. It has been evaluated in both dogs and humans. The wick method is more accurate and reproducible than a simple needle manometer or pressure probes[9,93]. It also allows the continuous measurement of ICP; other techniques that require the repeated insertion of needles cannot do this. However, the disadvantages of the wick technique are that coagulation may occur around the tip and the possibility of material from the wick being left in the insertion wound[94].

Simple needle manometry

Whitesides and co-workers[95] devised this technique which employs an 18-G needle and a simple mercury manometer. This is a simple method and the equipment should be readily available in most hospitals. The criticism of the needle technique is the need for injection of saline into the tissue during the reading which creates a disequilibrium, resulting in high readings at low pressures and low readings at high pressures[93]. High readings also occur if the needle is placed in a tendon or if the needle is pulled back aspirating a plug of muscle. This method is not accurate as the wick catheter[93].

Infusion technique

This technique was evaluated by Matsen and co-workers[28,74]. It uses a syringe infusion pump to infuse 0·7 ml saline per day via a 19-G needle and has been tried in both animal and human models. The pressure measurement was accurate to 2 mmHg (range 0·5–3 mmHg) and allowed continuous measurement of ICP. Because of the need for continuous infusion of saline, an increase ICP of 2–4 mmHg may occur, but this is small and is likely to be significant only in borderline cases[96].

Slit catheter

This was described by Rorabeck and co-workers[97] and the method was further modified by Barnes *et al.*[98]. The catheters were made from epidural catheter tubing, slits being made to reduce clotting problems. This system employs an infusion system and is thought to be easier to use than the wick catheter.

Central venous pressure manometer

In this technique an 18-G needle is attached to a simple central venous pressure manometer; it is similar to the simple needle technique[99]. The advantage is that it is quick and no special equipment is needed, although it suffers from the same inaccuracies as the simple needle manometer technique.

Side-ported needle

This allows the measurement of pressure in several compartments using the same needle, without the need to change needles or catheters as in the wick and slit catheter methods[100]. Moed and Thorderson[101] compared the slit catheter, side-ported needle and simple needle techniques in a canine model. The values obtained with the simple needle were consistently higher than those with the other two methods, a mean of 18·3 mmHg higher than with the slit catheter and 19·3 mmHg higher than with the side-ported needle. The disadvantage of the side-ported needle is that it cannot be used for continuous monitoring.

Fibreoptic transducer

This technique has been reported by Ovre and co-workers[27]. The advantage of this technique is that it is easy to use, allows continuous monitoring, there is no need for flushing and it does not require recalibration. However, it is very expensive.

Recommendations

All the above techniques allow the measurement of ICP and all have been used clinically. If specialized equipment is not readily available the simple needle connected to a central venous pressure manometer or a pressure transducer can be recommended. Otherwise the authors would recommend the side-ported needle, which allows the same needle to measure multiple compartments, or the wick catheter, which can be used for continuous monitoring.

Diagnosing compartment syndrome using intracompartmental pressure

As already noted ICP measurement is more important in the obtunded patient, in children, in those with equivocal signs and in those with multiple injuries[9,70]. However, even in the conscious patient, measurement of ICP can prevent delay in the diagnosis and treatment of compartment syndrome[17]. Monitoring of ICP in patients at risk of developing ACS has no significant complications while not monitoring may lead to a missed diagnosis[9,17,20,25,27,33,99,102]. A particular problem of measuring ICP is to ensure that the correct site is chosen for the measurement. The highest pressure is thought to occur in the deep posterior and the anterior compartment in the leg, and when the catheter is close to a fracture site (within 5 cm of the fracture line)[103]. Both the main compartments of the leg may need to be measured to avoid missing raised ICP.

Critical pressure for diagnosing compartment syndrome

Normal resting intramuscular pressure is 0–8 mmHg, and pain and paraesthesia first appear at pressures of between 20 and 30 mmHg[9]. Mubarak and co-workers[9,93] have used an ICP of more than 30 mmHg as a basis for performing fasciotomy, identifying that the critical ICP of 30 mmHg can be present only for a period of 6–8 h before irreversible changes occur[104].

Whitesides *et al.*[105] have suggested using a difference between the diastolic pressure and the ICP, with a differential pressure within 10–30 mmHg of the diastolic pressure as the threshold for performing a fasciotomy. This method was further assessed McQueen and Court-Brown[25] in 116 patients with tibial fractures; a differential pressure of 30 mmHg was used. They showed that fasciotomy was needed in only three patients, with no adverse sequelae in the others. However, if a simple threshold pressure of 30 mmHg had been used, 29–43 per cent would have required a fasciotomy, while a threshold pressure of 40 mmHg would have led to 23 per cent undergoing such surgery[25,27].

Others have used the delta pressure (difference between the mean arterial pressure and the ICP), with fasciotomy performed when this was less than 40 mmHg[77]. Matsen and co-workers[96] showed that patients varied in their tolerance to raised ICP before neuromuscular deficits occurred and used an ICP level of 45 mmHg for performing fasciotomy. Allen and colleagues[33] have used an ICP of 40 mmHg for observation and 50 mmHg for immediate decompression, with no adverse sequelae. Ouellette and Kelly[70] have used an ICP of between 15 and 25 mmHg when clinical signs were present and more than 25 mmHg in the absence of clinical signs as their threshold for performing fasciotomy, with 13 of 17 patients having a satisfactory result.

Recently, Janzing and Broos[102] applied seven different criteria for assessing the need for a fasciotomy in orthopaedic patients. They found that most of the criteria used by other authors would have led to many patients undergoing unnecessary surgery. They recommended measuring ICP only in symptomatic patients or in those difficult to assess. In the latter group, the use of a nerve stimulator along with ICP measurement may help to differentiate between compartment syndrome and direct nerve trauma[96]. The ideal pressure threshold for performing a fasciotomy is still not known. Because of the effect of blood pressure on the development of compartment syndrome, it may be more appropriate to use a differential pressure as advocated by Whitesides and co-workers[105], to prevent unnecessary fasciotomy.

Treatment

The primary treatment of LCS is decompression by fasciotomy. Other complications, such as renal failure as part of the crush syndrome, may require dialysis or plasma exchange[9,79,106]. Elevation of the limb is sometimes used as a temporary measure in an attempt to reduce ICP but this has no effect and may even increase the pressure in both upper and lower limb syndromes, adversely affecting the perfusion pressures[10,107]. In phlegmasia caerulea dolens, however, early aggressive limb elevation is of paramount importance, together with anticoagulation[64]. Treatment

Table 3 Effect of time on the results of fasciotomy

Reference	Year	Patients or limbs with compartment syndrome	Preoperative pressure for decompression (mmHg)	Time to decompression (h)	No. of patients with no significant adverse sequelae
Sheridan and Matsen[28]	1976	22	n.a.	< 12	15
		24	n.a.	> 12	2
Gelberman *et al.*[20]	1981	10	30	21 (6–48)	2
Rorabeck[3]	1984	18	28–47	1–48	13
Schwartz *et al.*[30]	1989	9	30–40	4 (0–16·3)	6
Fakhouri and Manoli[29]	1992	12	30	3–13	9
Georgiadis[16]	1995	10	30	6·8 (2·2–11·2)	9
Silas *et al.*[32]	1995	9	30	5 (2–8)	9
Ouellette and Kelly[70]	1996	17	25*	< 1 to > 24	13
McQueen *et al.*[17]	1996	23	30†	16 (4–28)	13
Wiger *et al.*[108]	1998	12	30‡	4 (1–12)	12
		11	54·6 (35–70)	32 (4–80)	1
Mullett *et al.*[19]	2001	10	n.a.	< 12	0
		7	n.a.	> 12	3

Values in parentheses indicate the range. *Pressure threshold if no clinical signs present, 15–25 mmHg pressure threshold if clinical signs present; †differential pressure of 30 mmHg; ‡delta pressure. n.a., Data not available

must be commenced as soon as possible to minimize complications (*Table 3*).

Fasciotomy

For adequate treatment one should consider decompression of all compartments. In the forearm there are two compartments, the volar and dorsal compartments. In the thigh there are three compartments, the anterior, posterior and medial. In the leg there are four recognized compartments, the anterior, lateral (or peroneal), the deep posterior and the superficial posterior. Diagrammatic representations of the compartments are shown in *Figs 1–3*.

The common types of fasciotomy are single- or double-incision fasciotomy, with or without fibular excision for the leg[109]. In the forearm[3,96,109] volar fasciotomy is usually the method of choice, but concurrent dorsal fasciotomy is also undertaken by some authors[20,21,70,96]. For compartment syndromes of the hand, the carpal tunnel is always decompressed in addition to other affected fascial compartments[70].

Cooper[110] has described the use of a single lateral incision for decompression of all four compartments of the leg which was used successfully in his series of six patients. Mubarak and Owen[111] have demonstrated that double-incision fasciotomy reduces ICP to within the normal range. However, fasciotomy using the fibulectomy technique may also produce good results if the entire length of the fibular periosteal bed is opened in each compartment[111]. The advantage of the double-incision technique is that there is no need for removal of bone, it is quicker and it carries less risk of damage to neurovascular structures, with adequate decompression of the posterior compartment. Patman[39] has advocated the fibulectomy technique only if there is severe trauma to the limb. The authors' preferred technique for fasciotomy incisions is shown in *Figs 1–3*. The techniques for the various fasciotomies have been summarized in a recent article by Janzing and Broos[112].

The fasciotomy incisions are either closed (using a small skin incision or with the skin closed primarily), subcutaneous (a limited skin incision with secondary closure) or open (an extensive skin incision with secondary skin closure). Jensen and Sandermann[89] compared subcutaneous and open fasciotomy. Five of 39 limbs that had subcutaneous fasciotomy still showed signs of LCS and all five patients required reoperation with long skin incisions; patients with open fasciotomies were deemed to have had adequate decompression. Those patients with prolonged periods of ischaemia (mean 38 h) eventually required an amputation. However, others have shown closed-incision or open fasciotomy to have no effect on the final result[28]. Patman[39] used multiple small skin incisions for decompression in fasciotomy for vascular causes. He advocated long skin incisions only if there was massive soft tissue swelling, paralysis or borderline function of muscles, or if muscle necrosis was encountered.

The length of the fasciotomy wound, using a double-incision technique, was evaluated by Cohen *et al.*[113]. A skin incision of 8 cm in length decreased the mean(s.d.) ICP from 48(12) to 25(11) mmHg. However, to decompress adequately all the compartments of the leg requires a longer incision of between 12 and 20 cm. This is because the skin may itself be a contributing factor in the increase in ICP.

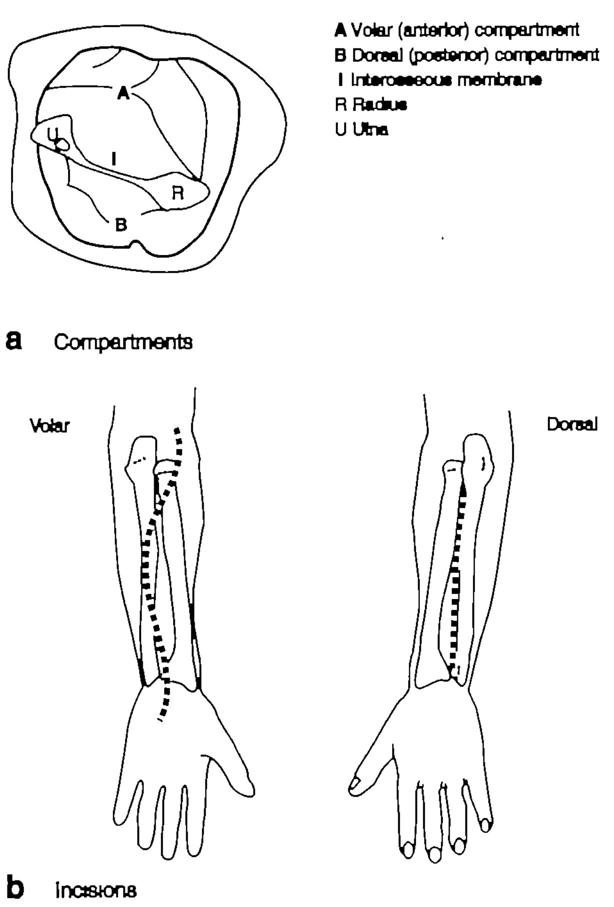


Fig. 1 a Compartments of the forearm. b Fasciotomy incisions in the forearm

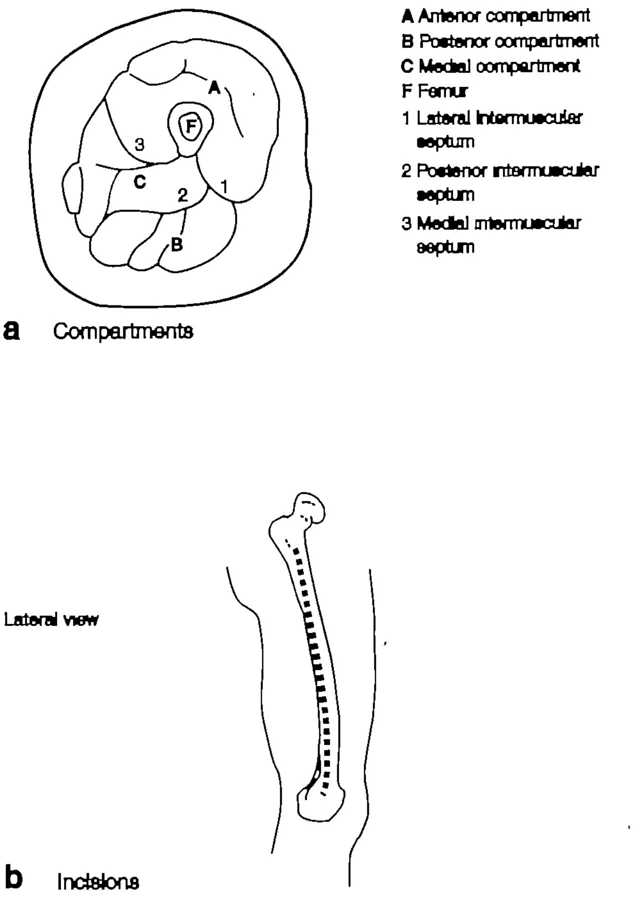


Fig. 2 a Compartments of the thigh. b Fasciotomy incisions in the thigh

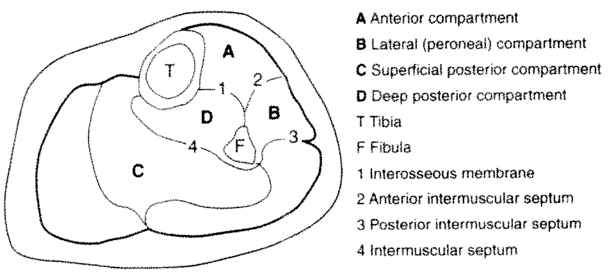
Mubarak and co-workers[9,111] used an incision 15 cm long and found that the skin incision alone reduced the ICP by 5–9 mmHg.

For adequate decompression, open fasciotomy is recommended. The skin incision in the leg should be approximately 16 cm. This is because small, subcutaneous and closed incisions may not decompress the compartments fully and patients so treated may need further intervention to normalize ICP.

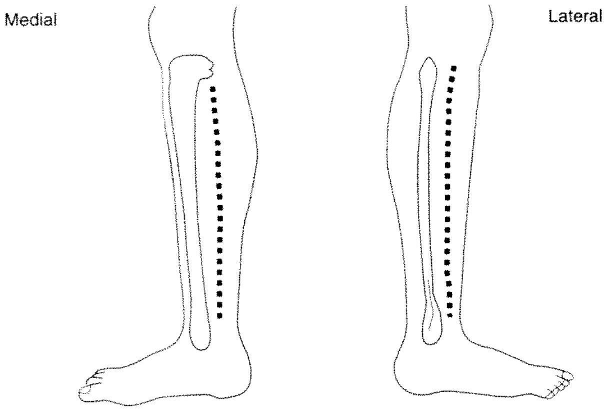
The fasciotomy wound may be allowed to heal by secondary intention or undergo skin closure (primary, delayed primary and secondary), skin grafting or flap coverage[15,28,52,89]. Early secondary wound closure after fasciotomy has been advocated for some patients on the third or fourth day after operation, but only with concurrent ICP monitoring because closing the wound even on the fourth day can still increase ICP[108]. Such early closure, however, avoids the need for skin grafting[108]. In one series, 77 per cent of patients with open fasciotomies required skin grafting[28]. Split-thickness skin grafting is usually performed after 7–21 days[22,52]. Subcutaneous fasciotomies can be treated by primary suture, whereas double incisions may require split-thickness skin grafting[89]. Both skin grafting and suturing by third intention can reduce hospital stay compared to healing by secondary intention[52].

Other authors have described techniques to avoid the need for skin grafting. These include employing plaster strips, rubber bands, skin staples and subcuticular non-absorbable sutures, all off which are used to close the wound slowly[114–117]. The plaster strips technique allows the patient to have wound closure completed in the outpatient setting[114]. Bail and co-workers[118] have described the use of a silicone sheet to cover the defect of fasciotomy. The sheet is sutured to the skin edges and this is slowly reduced in extent until the edges are closed. This allows skin closure within days and also avoids the need for skin grafting.

While some authors have described no major complications related to fasciotomy[22], others have described


T
A
1
2
D
B
4
F
3
C
A Anterior compartment
B Lateral (peroneal) compartment
C Superficial posterior compartment
D Deep posterior compartment
T Tibia
F Fibula
1 Interosseous membrane
2 Anterior intermuscular septum
3 Posterior intermuscular septum
4 Intermuscular septum

a Compartments



b Incisions

Fig. 3 **a** Compartments of the leg. **b** Fasciotomy incisions in the leg

increased rates of soft tissue infection, bone infection, amputation and renal failure[28,41,56]. Fitzgerald and co-workers[119], in a series of 60 patients followed up after fasciotomy, found that the most common complication was impaired sensation around the margins of the wound, with a significant proportion suffering from swollen limbs and tethered scars. Complications occur mainly after late fasciotomies, i.e. when LCS is present for more than 12 h, with a corresponding increase in the number of inpatient days[28]. Bermudez *et al.*[120] found that patients who have undergone fasciotomy have poor calf muscle function, without any evidence of venous obstruction or venous reflux. This eventually leads to chronic venous insufficiency and is an argument for not performing prophylactic fasciotomy.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy was evaluated initially in both normotensive and hypotensive dogs with LCS[121,122]. The treatment reduced oedema and muscle necrosis. The proposed mechanism is that hyperoxygenation increases both the supply of oxygen and causes vasoconstriction of blood vessels, which in turn reduces capillary blood pressure and decreases transudation[123,124]. It is advocated only as an adjunct to fasciotomy or when immediate surgical treatment in not possible. Bouachour and co-workers[125] reported 36 patients with crush injuries, half of whom received hyperbaric treatment after surgery with fasciotomy. The patients receiving hyperbaric oxygen had significantly better wound healing without tissue necrosis than those receiving placebo. Further work is needed to elucidate this treatment fully.

Drug therapy

Mannitol is a hyperosmolar diuretic that may reduce the incidence of LCS after revascularization[126–128]. It acts as a free radical scavenger and reduces oedema[126]. Mannitol has been shown to reduce postischaemic oedema and muscle necrosis in an animal model, although better results are still obtained by fasciotomy[126,129]. Mannitol was used prophylactically in 15 patients in one study and none went on to develop compartment syndrome[127], but ICP was not measured. In a non-randomized study Shah and co-workers[51] have also used mannitol in a series of patients and claimed a possible beneficial effect. Another free radical scavenger, superoxide dismutase, has shown variable results in animals[130] and its use in humans is not yet established[126].

Thromboxane A_2 is thought to be an important mediator in the development of oedema following reperfusion. In one study an inhibitor of thromboxane A_2 was used in an animal model, and ICP was significantly reduced in treated animals compared with controls[131]. No human trials are available. At present few studies are available on these adjunctive treatments to fasciotomy and, although all promise to be beneficial, more work in humans will be needed before their role becomes clear. The management of LCS is summarized in *Fig. 4*.

Abdominal compartment syndrome

This syndrome is characterized by a tensely distended abdomen, raised IAP, increased peak airway pressure, inadequate ventilation with hypoxia and hypercarbia, disturbed renal and cardiovascular function, and an improvement of these features after abdominal decompression[132,133]. Typically the diagnosis is made in severely ill patients, often in the intensive care unit, and haemodynamic status is improved immediately after decompression.

Pathophysiology

In ACS there is a compromise of cardiorespiratory and renal function despite adequate fluid resuscitation and ventilation. Harman and co-workers[134] demonstrated this in an animal model in which increasing IAP to 20 mmHg decreased the glomerular filtration rate and reduced urine output to a fifth of normal. An IAP of only 15–20 mmHg causes oliguria and an increase to 40 mmHg leads to anuria[134–136]. Increased IAP also causes decreased cardiac output and stroke volume, and increases systemic vascular resistance mainly due to a decrease in the cardiac preload. The mean arterial pressure remains unchanged[137]. Cardiac output improves with intravenous fluids while urine output does not, suggesting that the oliguria is due to a local effect on the kidney rather than ureteral compression[134,136]. Compression of the renal vein and the kidney is the most likely cause of renal failure in ACS, as opposed to renal or ureteral compression alone[138,139]. ACS also increases peak airway pressure and thoracic pleural pressure, thereby compromising ventilation in addition to decreasing cardiac output[140,141].

Aetiology

The common causes of ACS are blunt and penetrating trauma to the abdomen, often with liver, vascular and splenic damage[142–144]. It is more likely to develop if there is both abdominal and pelvic trauma[143]. Packing used for uncontrolled haemorrhage is also a risk factor for developing ACS[145]. Patients undergoing repair of abdominal aortic aneurysm (AAA), whether electively or as an emergency, as well as other types of elective abdominal surgery are also at risk of developing ACS[136,141]. The syndrome is, however, most often encountered after repair of ruptured AAA.

ACS may also occur after burns and should be suspected as a cause of renal failure despite adequate fluid resuscitation[146–148]. Secondary ACS has been found in patients with non-abdominal injuries[149]. These patients have dilated bowel loops but no sign of intra-abdominal trauma. A possible explanation may be an adverse effect of vigorous fluid resuscitation, although this remains unproven. Extraperitoneal injuries followed by high levels of peak expiratory end pressure and intrathoracic pressure may also lead to ACS[150]. The risk of developing ACS increases with increase in Injury Severity Score[142,151], and is between 5·5 and 32·8 per cent following abdominal surgery or trauma[143,145,151,152]. After repair of ruptured AAA it is 3·8 per cent[141].

Symptoms and signs

Because affected patients are often in the intensive care unit and on ventilatory support, symptoms are frequently not apparent. Signs of compartment syndrome include a tense abdomen, cardiorespiratory compromise in the absence of hypovolaemia, and oliguria or anuria. Clinical abdominal

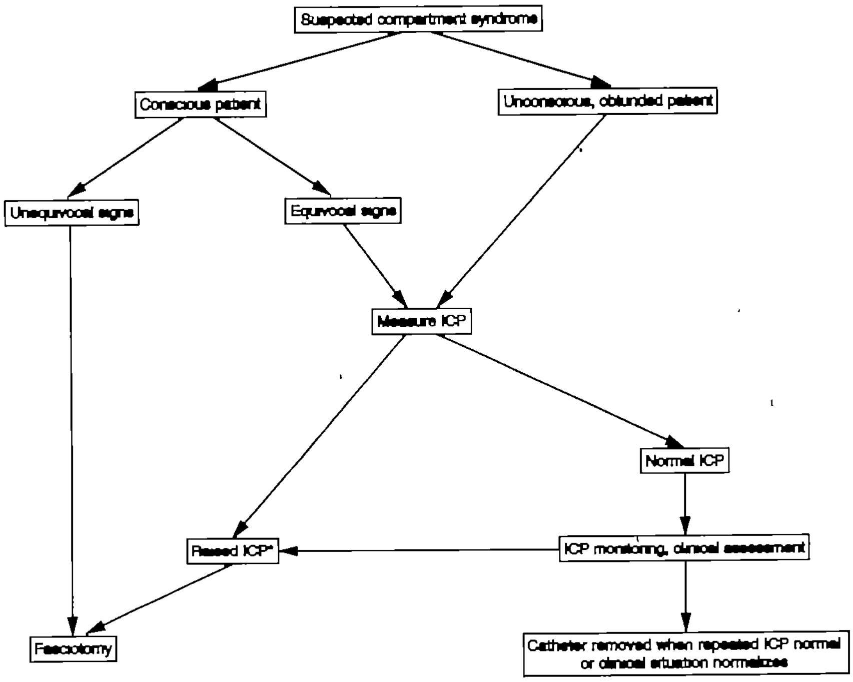

Suspected compartment syndrome
Conscious patient
Unconscious, obtunded patient
Unequivocal signs
Equivocal signs
Measure ICP
Normal ICP
ICP monitoring, clinical assessment
Raised ICP*
Fasciotomy
Catheter removed when repeated ICP normal or clinical situation normalizes

Fig. 4 Management of acute limb compartment syndrome. *Difference of less than 30 mmHg between diastolic pressure and intracompartmental pressure (ICP)

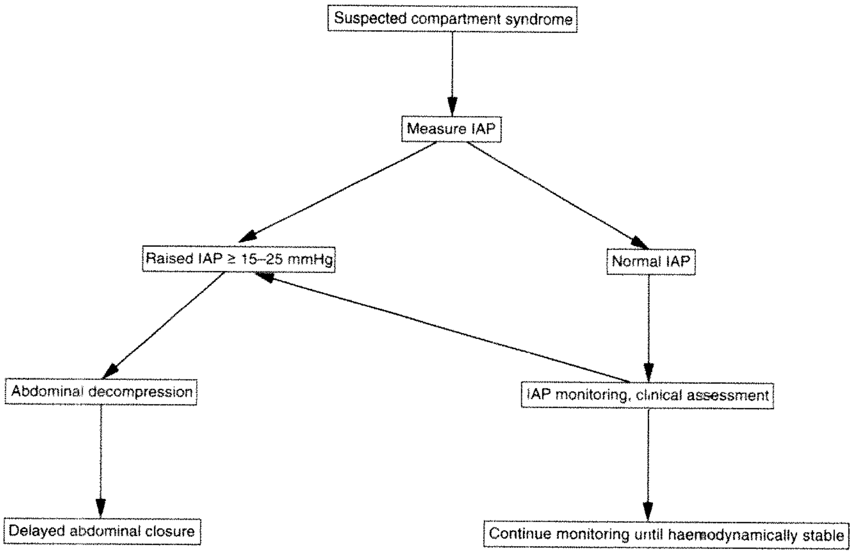

Suspected compartment syndrome
Measure IAP
Raised IAP ≥ 15–25 mmHg
Normal IAP
Abdominal decompression
IAP monitoring, clinical assessment
Delayed abdominal closure
Continue monitoring until haemodynamically stable

Fig. 5 Management of abdominal compartment syndrome. IAP, intra-abdominal pressure

examination is not thought to be reliable for detecting raised IAP[153]. Pickhardt and co-workers[154] have described computed tomography findings in four patient with ACS, two with pancreatitis and two with trauma. All four patients had compression of the inferior vena cava, round belly sign (increased ratio of anteroposterior to transverse abdominal diameter greater than 0·80) and ascites or haemoperitoneum. Low gastric mucosal pH may also suggest early ACS, allowing early decompression[151].

Measuring intra-abdominal pressure

The ideal technique for measuring IAP would be to insert a catheter directly into the peritoneal cavity. However, it has been shown that transurethral bladder pressure reflects the IAP indirectly[137]; bladder pressure measurement avoids the risks of inserting a cannula into the peritoneal cavity itself. Kron and co-workers[155] have popularized this technique. More recently, Johna *et al.*[156] have used the bladder catheter method and found that in the range of 0–15 mmHg bladder pressure does not always correlate with raised IAP. Nevertheless, this method remains the most commonly used. Normal IAP in postoperative surgical patients lies between 3·5 and 10·5 mmHg in men, and 3·0 and 8·8 mmHg in women[157].

Ivatury and co-workers[151] diagnosed ACS if IAP was above 25 cmH_2O. Kron *et al.*[155] treated patients with an IAP of less than 25 mmHg medically; those with an IAP above 25 mmHg developed renal insufficiency and subsequently had a laparotomy with recovery of renal function. Ertel and colleagues[143] also found that patients with an IAP below 25 mmHg did not develop ACS while those with a higher IAP did. In the light of this, an IAP greater than 15–25 mmHg may be considered to be diagnostic of ACS. However, it must be emphasized that the use of IAP measurement to diagnose ACS should be in the setting of cardiorespiratory and renal impairment[136,143–145,155,158].

Treatment

The treatment of ACS is decompression of the abdomen[159], following which there is an immediate improvement in haemodynamic status[135]. It is generally appropriate to leave the abdominal wound open to prevent further development of ACS. Interestingly, Cheatham and co-workers[144] have reported, in a series of 22 patients whose abdomens were left open prophylactically, that 11 still went on to develop ACS. The reason for this is not explained by the authors but may be due to oedematous loops of bowel caused by vigorous fluid resuscitation[149]. Mayberry and colleagues[160] found that the majority of surgeons in the USA were unlikely to perform primary closure of the abdomen for trauma if there was pulmonary deterioration, haemodynamic instability, massive oedema, planned reoperation, packing, or tight closure. In patients with abdominal and chest trauma both the chest and the abdomen can be left open if the patient is unstable[161,162]. Many techniques have been described for temporarily covering the abdomen, including a mesh[145,151,158,163,164], a plastic bag[145,164,165], fascial closure[145,151], plastic or silicone sheets[159,166] and a vacuum pack[167]. Others have used skin clips to achieve skin closure while leaving the muscle and fascial layer open[145,165]. The general management of ACS is summarized in *Fig. 5*.

Outcome

The mortality rate associated with this condition is significant, lying between 63 and 72 per cent, the poor outcome reflecting not only the development of ACS but also the concomitant injury[142,145,152]. Morbidity is also significant and is often related to abdominal closure.

The problem with mesh closure is the subsequent difficulty in removing the mesh and obtaining full closure; the wound is often left to heal by secondary intention which leads to the development of ventral hernia in up to 63 per cent of patients[163,164] and occasionally to bowel fistulas[145,151,158,164,167]. However, mesh closure carries a lower incidence of multiorgan dysfunction, further ACS and death than fascial closure, and the incidence of bowel fistula reduces with operator experience[151].

Sherck and co-workers[166] have described a technique that involves placing omentum in the base of the wound which is then covered with sterile plastic or silicone sheets. Two operating drapes are placed over this. When access to the abdomen is no longer required, the fascia is closed. The skin is closed by delayed primary or secondary closure. This method was reported in 50 patients of whom four had established ACS. Thirty-two survived to full closure and in 28 of these the abdomen was closed within 72 h. No patient developed ACS after operation. In a further series of 18 patients who had prophylactic non-absorbable prosthetic mesh closure of the abdomen after repair of a ruptured AAA or abdominopelvic trauma, only one developed ACS[158]. Delayed primary closure was possible in 16 of the 18 patients. In another study a vacuum pack technique allowed 21 of 28 patients to undergo successful full or staged closure[167].

Other workers have compared prophylactic mesh closure at initial laparotomy with mesh closure at a second laparotomy[163]. The reasons for prophylactic primary mesh closure were planned reoperation, ACS, abdominal wall defect, necrotizing fasciitis and a tight abdomen. The patients who underwent prophylactic primary mesh closure had a significantly lower incidence of ACS, necrotizing fasciitis and intra-abdominal abscess formation. After abdominal decompression and temporary closure there is significant fluid loss, often exceeding several litres[132]. If a plastic bag is used, it is important either to have suction drains to remove the fluid or a plastic stoma bag placed over a perforation in the plastic. This should be attached to a closed drainage system.

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Randomized clinical trial assessing the side-effects of glyceryl trinitrate and diltiazem hydrochloride in the treatment of chronic anal fissure

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Introduction: Glyceryl trinitrate (GTN) ointment (0·2 per cent) has an efficacy of up to 68 per cent in healing chronic anal fissure, but with headache as a major side-effect. Diltiazem hydrochloride (DTZ) cream (2 per cent) is expected to have fewer side-effects.
Methods: A prospective double-blind randomized two-centre trial requiring at least 26 patients in each group ($\alpha = 0\cdot05$, $\beta = 0\cdot9$) was instituted after approval of the local ethics committee, to compare the incidence of side-effects (primary endpoint) with 0·2 per cent GTN ointment and 2 per cent DTZ cream in the treatment of chronic anal fissure. Treatments were applied perianally, twice daily for 6–8 weeks. All patients gave written informed consent.
Results: Both groups were comparable in patient demographics and clinical characteristics. Twelve patients violated the protocol, withdrew or did not attend follow-up. There were more side-effects with GTN (21 of 29 patients) than with DTZ (13 of 31) (relative risk (RR) 1·84 (95 per cent confidence interval (c.i.) 1·11 to 3·04), $P = 0\cdot01$). In particular, more headaches occurred with GTN (17 of 29 patients) than with DTZ (eight of 31) (RR 2·06 (95 per cent c.i. 1·18 to 3·59), $P = 0\cdot01$). There were no significant differences in healing and symptomatic improvement rates between patients receiving GTN (25 of 29) and DTZ (24 of 31).
Discussion: DTZ cream caused substantially fewer headaches than GTN ointment. There was no significant difference in the healing or improvement of chronic anal fissure between the treatments. DTZ may be the preferred first-line treatment for chronic anal fissure.

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Introduction

Anal fissure is a common medical problem. It afflicts both sexes equally. It is characterized by pain and rectal bleeding[1,2]. The treatment of acute anal fissure is conservative with application of topical ointments, managed mainly in the primary care setting[3]. However, the standard treatment for chronic anal fissure (defined as symptoms lasting for more than 8–12 weeks, with horizontal muscle fibres showing at the fissure base and/or the presence of a sentinel tag) has been lateral sphincterotomy[4] or, rarely, anal dilatation. Both of these treatments cause significant short- and long-term morbidity with incontinence rates of up to 30 per cent[5,6].

The ischaemic nature of chronic anal fissure is due to high resting anal pressure[7]. This theory is now widely accepted as the cause for chronicity of these fissures, and various medical therapies have now been introduced to reduce the resting anal pressure and so improve the blood supply to the affected anoderm and thus enhance healing. The agents used have been glyceryl trinitrate (GTN) ointment[8–10], botulinum toxin[11], nifedipine[12,13], diltiazem hydrochloride (DTZ) and bethanechol[14–16]. All of these treatments have been shown uniformly to reduce the mean maximum resting anal pressure by 23–30 per cent. Botulinum toxin, which has to be injected locally, has the advantage of being a once-only treatment, but economic and technical aspects have prevented its widespread acceptance. GTN has been studied most extensively in various series and randomized controlled trials[8,9,17]. It has an efficacy of 68 per cent when used as a 0·2 per cent ointment[9], but headaches are a major side-effect. Oral nifedipine[13] and oral DTZ[18] also cause headaches and postural hypotension. Topical 2 per cent DTZ cream holds the promise of causing few or no side-effects[14–16] while being equally efficacious in reducing the mean maximum resting anal pressure. In this study, comparing 0·2 per cent GTN ointment with 2 per cent DTZ cream, the primary endpoint was the relative incidence of side-effects of treatment. Secondary endpoints were the efficacy of treatment and early recurrence.

Patients and methods

Patients

Consecutive adult patients with symptomatic chronic anal fissure were enrolled in the study, after approval had been obtained from the local ethics committee and the Medicines Control Agency. One of the centres (Queen Elizabeth Hospital) is a rural hospital and the other (King's College Hospital) is an inner-city urban teaching hospital. The inclusion and exclusion criteria are listed in *Table 1*. All patients gave fully informed written consent, and were supplied with an information leaflet and counselled regarding headaches. They were allowed to withdraw from the trial at any time, without stating a reason.

Study design

Eligible patients were assigned randomly to one of the two treatment groups according to a computer-generated list to allow block randomization managed by the clinical trials pharmacist and coordinated at a single centre. During the trial, the randomization code was not available to the investigators assessing the patients.

The chosen primary endpoint for the study was the incidence of side-effects (headaches). From previous studies, it was assumed that the expected proportion of patients experiencing headache as a side-effect would be 58 per cent for 0·2 per cent GTN ointment[9]. While previous studies with 2 per cent DTZ cream have not reported any headaches[14], it was assumed that up to 10 per cent of patients might experience headaches with 2 per cent DTZ cream. With these assumptions, a study with a significance level (α) of 0·05 and a power (β) of 0·9 would require 52 patients (26 in each group) according to the Altman nomogram[19]. Secondary endpoints were rates of healing and symptomatic improvement and of early recurrence.

At 3, 6, 9 and 12 weeks of follow-up, an examiner, unaware of the treatment assignments, evaluated the outcome clinically and by use of a visual analogue pain score. The treatment was considered successful if the fissure had healed. Persistence of the fissure in the absence of symptoms was considered to be symptomatic improvement. Pulse and blood pressure readings were taken at each visit and all side-effects were recorded. Side-effects were graded as unlikely, possibly, probably or definitely related to the treatment.

Baseline assessment

All patients underwent a pretreatment evaluation that included clinical inspection of the fissure, proctoscopy and sigmoidoscopy. If this was not possible at the first visit because of pain, it was completed at a subsequent visit. Any suspicion of another medical condition directly or indirectly affecting the diagnosis or treatment led to further investigations.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	
Diagnosis of chronic anal fissure (anterior or posterior midline) was based on presence of two of the following three criteria:	
1	Pain after defaecation lasting for more than 3 months (with or without bleeding, pruritus and/or discharge)
2	Presence of sentinel anal tag
3	Exposure of the horizontal fibres of the internal anal sphincter
Exclusion criteria	
1	Patients with acute fissure
2	Fissure associated with other conditions (e.g. inflammatory bowel disease, anal cancer, tuberculosis)
3	Women who were pregnant or lactating or wishing to be pregnant (not on adequate contraception and in childbearing age group)
4	Patients with significant cardiovascular conditions

Treatment

The 0·2 per cent GTN ointment or 2 per cent DTZ cream (SLA Pharma, Watford, UK) was supplied to patients in identical tubes weighing 30 g. Compliance checks were done by weighing the tubes at each visit. Patients applied the allocated treatment by fingertip to the anus (anal verge) twice daily for 6 weeks as instructed verbally and in writing. If, at 6 weeks, the treatment was considered to have improved but not to have healed the fissure, a further 2 weeks of the same treatment was given and the patient was seen at 8 weeks.

Clinical care, follow-up and outcome measures

At each 3-weekly visit, patients were asked whether they wanted to continue in the study. Those who did not want to continue at any point were offered lateral internal sphincterotomy. If the fissure persisted at the 6-week evaluation, the examiner could decide to offer the patient lateral internal sphincterotomy. Non-attenders were contacted by post or telephone. Patients who wished to discontinue treatment were deemed non-compliant.

Statistical analysis and reporting

Statistical analyses were carried out by Cochran–Mantel–Haenszel test and Wilcoxon signed rank sum test where appropriate, on an intention-to-treat basis. Relative risk (RR) with 95 per cent confidence intervals (95 per cent c.i.) for development of side-effects and improvement on treatment were determined. The report was prepared in accordance with the revised CONSORT statement[20].

Results

Between January 2000 and January 2001, 61 consecutive patients (one ineligible) with chronic anal fissure were enrolled; 29 patients (15 women; median (range) age 39 (21–73) years) were randomly assigned to receive 0·2 per cent GTN ointment, and 31 patients (20 women; median (range) age 45 (21–73) years) received 2 per cent DTZ cream (*Fig. 1*). All the patients reported severe pain after defaecation with or without rectal bleeding, discharge and/or pruritus, and each had a posterior or anterior anal fissure with a large sentinel tag of skin and/or exposure of fibres of the internal anal sphincter. The groups were similar with regard to age, sex, and duration and nature of symptoms (*Table 2*).

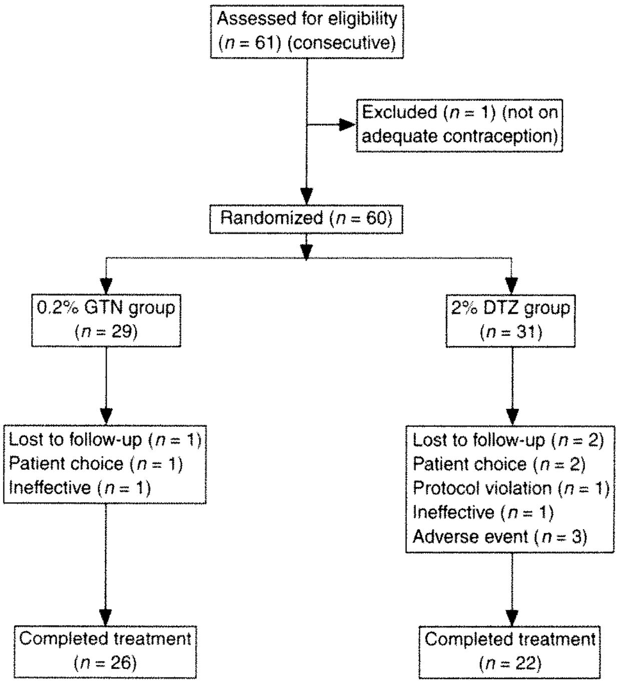

Fig. 1 Study flow chart. All analyses were done on an intention-to-treat basis. GTN, glyceryl trinitrate; DTZ, diltiazem hydrochloride

Table 2 Patient demographics and symptom profile

	GTN (*n* = 29)	DTZ (*n* = 31)
Median (range) age (years)	39 (21–73)	45 (21–73)
Sex ratio (M : F)	14 : 15	20 : 11
Median duration of symptoms (weeks)	46	51
Pain	29	31
Bleeding	22	24
Anal pruritus	21	23
Discharge	12	13

GTN, 0·2 per cent glyceryl trinitrate; DTZ, 2 per cent diltiazem hydrochloride

Primary and secondary endpoints

After 6–8 weeks of treatment, 21 of 29 patients in the 0·2 per cent GTN group experienced side-effects, compared with 13 of 31 in the 2 per cent DTZ cream group (RR 1·84 (95 per cent c.i. 1·11 to 3·04), $P = 0{\cdot}01$). Headaches occurred in 17 of 29 patients in the GTN group, compared with eight of 31 in the DTZ group (RR 2·06 (95 per cent c.i. 1·18 to 3·59), $P = 0{\cdot}01$). Other side-effects are reported in *Table 3*. There was less pain in both groups during treatment, with no

Table 3 Side-effect profile

	GTN ($n = 29$)	DTZ ($n = 31$)
Headaches	17	8
Gastrointestinal effects*	9	3
Pruritus ani	2	3
Other	3	3
Total	21	13

*Abdominal pain, nausea, vomiting, diarrhoea. GTN, 0·2 per cent glyceryl trinitrate; DTZ, 2 per cent diltiazem hydrochloride

significant differences between the groups at any point during the study (*Fig. 2*). At 8 weeks, 25 of the 29 patients in the GTN group were deemed to be healed ($n = 12$) or improved ($n = 13$), compared with 24 of the 31 patients in the DTZ group (eight healed, 16 improved) (RR 0·69 (95 per cent c.i. 0·39 to 1·22), $P = 0.21$).

Other parameters

On comparing the two groups at various time intervals during the treatment period, there was no difference in change in the pulse rate or diastolic blood pressure from the baseline readings. In contrast, there was a difference in change of systolic blood pressure between patients receiving DTZ cream and GTN ointment at 6 weeks ($P = 0.03$; Wilcoxon rank sum test) and 8 weeks ($P = 0.05$). Those receiving DTZ cream showed a decrease in systolic blood pressure by a mean of 5·5 mmHg at 6 weeks and 6·2 mmHg at 8 weeks, while those receiving GTN ointment showed a rise of 3·6 and 1·6 mmHg respectively. There was no change in the systolic blood pressure at 3 weeks of treatment when the two groups were compared.

Follow-up

At the 12-week visit, two patients had recurrence after healing in the GTN group, whereas none of the patients in the DTZ group had such recurrence.

Discussion

This study shows that patients who applied 2 per cent DTZ cream for the treatment of chronic anal fissure experienced fewer side-effects (headaches and gastrointestinal side-effects) than patients applying 0·2 per cent GTN ointment, although the therapeutic efficacy was similar for both preparations. Headaches were not reported in a previous case series using DTZ[14], but neither were they reported in the initial case series using nitrates[17,21]; they became apparent only in later randomized controlled trials. Nevertheless, the number of headaches reported was significantly fewer than with the GTN group and, in addition, only two of eight patients in the DTZ group reported moderate to severe headaches, compared with eight of 17 patients receiving GTN. Two case series of 71 and 39 patients using DTZ in a much higher concentration have also reported the occurrence of headaches[15,16].

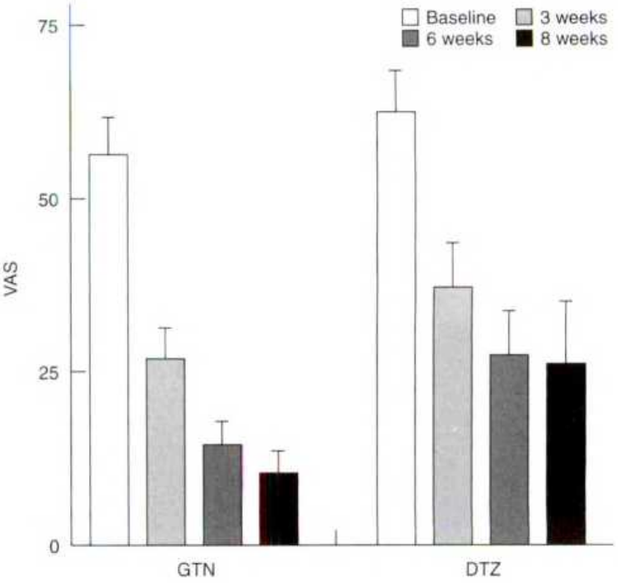

Fig. 2 Pain scores: reduction in visual analogue scale (VAS; 0–100 mm) scores during the treatment period. Values are mean(s.e.m.). There was no difference between the two treatment groups at any point during the treatment period ($P \geq 0.24$, Wilcoxon signed rank sum test)

Non-specific gastrointestinal side-effects are known to occur among patients using GTN for cardiovascular purposes[22]. In the present study, three patients in the DTZ group reported perineal itching or pruritus severe enough for them to discontinue treatment. The reason for this is not known. However, rashes or dermatitis have been reported in nearly 1 per cent of patients using DTZ and/or GTN for cardiovascular purposes[22]. It could be speculated that it may be the cream formulation or perhaps sphincter relaxation that resulted in perineal soiling. However, none of these patients reported any incontinence. Others have also reported perianal itching in a range of 6–7·5 per cent with DTZ application[15,16].

In this trial there was no significant difference between the treatments in terms of healing or symptomatic improvement rates. Other investigators have reported that treatment for more than 8 weeks results in better healing rates[15], but these remain inferior to surgical sphincterotomy, which is the treatment of choice for patients who do not improve with pharmacological internal anal sphincter relaxation.

Early recurrence will presumably remain a problem with all methods of pharmacological sphincter relaxation, as the anal resting pressure may revert to pretreatment levels on stopping treatment, and further trauma to the anoderm is likely to produce recurrence. However, the side-effect profile of 2 per cent DTZ cream suggests that it may become the preferred first-line treatment for chronic anal fissure.

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Randomized clinical trial of long-term outcome after resection of hepatitis C virus-related hepatocellular carcinoma by postoperative interferon therapy

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Background: Interferon therapy seems to decrease the incidence of recurrence after resection of hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC). Effects of postoperative interferon therapy on the survival rate after resection of such HCC are still unclear.
Methods: A prospective randomized clinical trial of postoperative interferon therapy was performed. Thirty men were allocated randomly after liver resection to an interferon-α group (15 patients) or a control group. Patients in the interferon group received interferon-α 6 MIU intramuscularly every day for 2 weeks, then three times a week for 14 weeks and finally twice a week for 88 weeks.
Results: The response to interferon was complete in two patients, there was a biochemical response in six patients and no response in seven patients. Interferon administration was not completed in three patients because of adverse events. Liver function did not change or worsened after operation in the control group, and did not change or improved in the interferon group. The cumulative survival rate was higher in the interferon group than in the control group ($P = 0{\cdot}041$).
Conclusion: Postoperative interferon therapy seems to improve the outcome after resection of HCV-related HCC.

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Introduction

The outcome after treatment for hepatocellular carcinoma (HCC) related to hepatitis C virus (HCV) is still unsatisfactory because of a high rate of recurrence of the carcinoma and progression of underlying liver disease such as chronic hepatitis or cirrhosis[1,2]. Previous prospective randomized controlled studies have shown that interferon-α helps to prevent the development of HCC in patients with HCV-related cirrhosis[3], and that postoperative interferon therapy seems to decrease the incidence of recurrence after resection of HCV-related HCC[4]. Recently, interferon was found to prevent worsening of compensated cirrhosis as well as inhibiting the development of HCC, increasing the survival rate[5]. Patients in the previous trial[4] continue to be monitored; the effects of postoperative interferon therapy on the outcome after resection of HCV-related HCC at 7 years 6 months are now reported.

Patients and methods

Trial profile

A trial of postoperative interferon therapy was initiated to investigate whether this therapy prevents recurrence of HCC after resection of the primary HCC[4]. Before the trial started, it was predicted that there would be a 75 per cent incidence of HCC recurrence in the control group over a 5-year observation period after operation, based on clinical experience[1,6]. It was also calculated that 15 patients in each group (interferon and control) would be needed for a two-sided α significance of 0·05 and a power of 0·80, giving a total risk reduction of two-thirds in the interferon group. The previous study showed that postoperative interferon therapy seems to decrease the incidence of recurrence of HCC after operation. The protocol of the present study was described earlier[4] and the 30 patients are the same. Thirty

Table 1 Patient demographic and clinical characteristics

	Interferon group (n = 15)	Control group (n = 15)
Mean(s.d.) age (years)	61·9(5·8)	60·0(4·8)
Sex (male)*	15 (100, 78, 100)	15 (100, 78, 100)
Alcohol abuse*	4 (27, 8, 55)	5 (33, 12, 62)
Child–Pugh score A*	11 (73, 45, 92)	12 (80, 52, 96)
Albumin (g/l)†	36 (33, 43)	36 (33, 41)
ALT (units/l)†	105 (45, 131)	86 (58, 151)
α-Fetoprotein (⩾ 100 μg/l)*	4 (27, 8, 55)	4 (27, 8, 55)
Tumour size (cm)†	2·5 (1·9, 3·5)	2·6 (2·4, 3·5)
Differentiation of tumour*		
Well differentiated	1 (7, 0, 32)	2 (13, 2, 40)
Moderately differentiated	11 (73, 45, 92)	11 (73, 45, 92)
Poorly differentiated	3 (20, 4, 48)	2 (13, 2, 40)
Grade (Histological activity index)*		
1	4 (27, 8, 55)	1 (7, 0, 32)
2	6 (40, 16, 68)	7 (47, 21, 73)
3	5 (33, 12, 62)	7 (47, 21, 73)
Cirrhosis*	7 (47, 21, 73)	8 (53, 27, 79)
HCV genotype*		
1a	0 (0, 0, 22)	0 (0, 0, 22)
1b	12 (80, 52, 96)	10 (67, 38, 88)
2a	3 (20, 4, 48)	4 (27, 8, 55)
2b	0 (0, 0, 22)	1 (7, 0, 32)
Viral load (⩾ 1·0 mEq/ml)*	7 (47, 21, 73)	8 (53, 27, 79)

*Values are numbers of patients (point estimation and 95 per cent confidence interval); †values are median (10th and 90th percentile). The histological activity index, with its published modifications[8], was used for expression of the severity of active hepatitis and degree of fibrosis in non-cancerous hepatic tissue. A histological activity index (components 1–3) of 0 indicated no activity (grade 0), scores of 1–3 indicated minimal activity (grade 1), scores of 4–8 indicated mild activity (grade 2), scores of 9–12 indicated moderate activity (grade 3) and scores of 13 or more indicated severe activity (grade 4). ALT, alanine aminotransferase. HCV, hepatitis C virus

male patients were randomly allocated after resection of HCC to an interferon-α group (15 patients) or a control group (15 patients). Randomization was by a random-numbers table. Criteria for eligibility were (1) a single tumour less than 5 cm in maximum diameter seen by preoperative imaging; (2) detectable HCV RNA without hepatitis B surface antigen or human immunodeficiency virus antibodies; (3) chronic hepatitis or a Child–Pugh score of A or B[7] for compensated cirrhosis; and (4) no severe thrombocytopenia (defined as a platelet count of less than 50×10^9 cells/l). Clinical characteristics and laboratory test results were similar in the two groups, as were the operative procedures (*Table 1*). Most variables in patients who were eligible for this trial but declined to participate were similar to those in the enrolled patients[4].

This study was undertaken in accordance with the Helsinki Declaration and was approved by the ethics committee of the institutions. Written informed consent was obtained from each patient.

Interferon treatment

Patients in the interferon group received 6 MIU interferon-α (human lymphoblastoid interferon; Sumiferon, Sumitomo Pharmaceuticals, Osaka, Japan) intramuscularly every day for 2 weeks, then three times weekly for 14 weeks and finally twice weekly for 88 weeks. Interferon therapy was started 5–15 (mean 9) weeks after operation. In one of the 15 patients treatment was started 7 months after operation at the request of the patient. No patient in the control group received postoperative treatment for carcinoma or liver disease up to the detection of recurrence; no patient in the interferon group received chemotherapy or any treatment other than interferon administration before detection of a recurrence.

Laboratory tests were done at least once a month during interferon therapy and at least once every 3 months after the end of therapy for evaluation of the response to therapy and identification of side-effects of interferon. Serum HCV RNA was detected by a method reported previously[3] and the viral load was measured by a branched DNA probe assay (Quantiplex HCV-RNA; Chiron, Emeryville, California, USA). A complete response was defined as the absence of serum HCV RNA and a serum alanine aminotransferase (ALT) activity within the reference range (less than 45 units/l) for at least 6 months after interferon therapy (in other words, viral and biochemical remission)[3]. A biochemical response was defined as a decrease in serum ALT activity to normal but with persistent detection of serum HCV RNA. No response was defined as a lack of decrease in ALT activity and persistence of HCV RNA.

Detection and treatment of recurrence

The serum concentrations of α-fetoprotein and protein induced by vitamin K absence and antagonist II were measured within 2 months after operation and every 3 months thereafter. Ultrasonography, computed tomography, magnetic resonance imaging or a combination of these was performed within 2 months after operation and every 3 months thereafter. When tumour recurrence was suspected on the basis of tumour markers, imaging or both, angiography or a biopsy under ultrasonographic guidance (or both) was done to establish a definitive diagnosis. Tumour markers and imaging were evaluated by physicians or radiologists who were blinded to the trial. Treatment methods for the recurrence were decided on the basis of the number and location of the recurrent tumour(s) and the results of liver function tests. When there were one or two recurrent tumours, ablation therapy such as resection and microwave coagulation therapy was considered first. When multiple recurrent tumours were found or when ablation therapy would be difficult because of the location of the recurrent tumour(s) or liver function, transarterial therapy (transcatheter arterial embolization and hepatic arterial infusion chemotherapy) was performed.

Statistical analysis

The results of preoperative laboratory tests and tests done when a recurrence was detected or at the study endpoint (7 years 6 months after the start of this trial) in patients without recurrence were compared because the treatment for recurrent HCC might affect the liver function tests. The laboratory test results were also compared at the detection of recurrence or the study endpoint, and at the time of detection of recurrence, between the two groups. The Mann–Whitney U test was used to evaluate differences in the laboratory results. Time to death was defined as the time from resection until death. Cumulative survival rates (which included data on patients who did not start or did not complete interferon therapy in the interferon group) were calculated by the Kaplan–Meier method, and the significance of differences between groups was assessed by the log rank test. All analyses were done with SAS statistical software (version 6.12; SAS Institute, Cary, North Carolina, USA).

Results

The median follow-up (from operation until death or the study endpoint) was 1817 (25th and 75th percentiles 1579 and 2008) days for patients receiving interferon-α and 1487 (1194 and 2055) days for the controls. As previously reported[4], interferon therapy could not be started in one patient because of premature ventricular contractions, and interferon administration could not be completed in three patients because of depression (one patient, at 17 days), severe general fatigue (one patient, at 11 months) and renal abscess (one patient, at 10 months; this patient also was found to have a recurrence in the same month). The administration of interferon was stopped prematurely in four patients with recurrence so that the tumour could be treated. In the interferon group, two patients were complete responders, six were biochemical responders and the other seven patients were non-responders. In control patients the serum ALT activity after operation (except immediately after surgery) was higher than the reference range and serum HCV RNA was detected at the follow-up appointments.

Intrahepatic recurrence was detected in nine patients in the interferon group and in 13 control patients by the study endpoint ($P = 0·055$, log rank test). At the time when recurrence was detected, eight patients in the interferon group and seven patients in the control group had one or two recurrent tumours. One patient in the interferon group and six control patients had three or more recurrent tumours. Ablation therapy was applied in six patients in the interferon group and in six control patients. Transarterial therapy was used in three patients in the interferon group and in six control patients. One patient in the control group could not undergo radical treatment (ablation therapy) because of worsened liver function. In addition, one patient in the control group could not undergo any treatment for recurrent tumours because of decompensation; he died within 4 months after the detection of the first multiple recurrences. For three of the four patients in whom a recurrence was detected during interferon therapy, therapy was completed after treatment of the recurrent tumour at the request of the patient.

In the interferon group the serum concentration of albumin had increased ($P = 0·038$) whereas the serum concentration of total bilirubin and the ALT activity had decreased by the time of detection of recurrence or the study endpoint ($P = 0·044$ and $P = 0·002$ respectively). In the control group, the serum concentration of total bilirubin had increased ($P = 0·044$); the serum concentration of albumin and ALT activity were unchanged. At the time of detection of recurrent tumour or the study endpoint, the serum concentration of albumin was higher in the interferon group than in the control group ($P = 0·014$), whereas the serum concentration of total bilirubin and the ALT activity was lower in the interferon group than in the control group ($P = 0·001$ and $P = 0·007$ respectively) (*Table 2*).

At the time of detection of recurrence, the median serum concentration of albumin was 40 g/l in the interferon group and 37 g/l in the control group ($P = 0·052$) (*Table 3*). The total bilirubin concentration was significantly lower in the interferon group than in the control group ($P = 0·044$).

Three patients in the interferon group and nine patients in the control group died; all patients who died had recurrence of HCC. After treatment of recurrence, 11 patients in the interferon group were alive without HCC at the study endpoint compared with only two patients in the

Table 2 Results of laboratory tests performed at the time of detection of recurrence or the study endpoint

	Interferon group ($n = 15$)	Control group ($n = 15$)	P*
Albumin (g/l)	41 (36, 51)	37 (28, 42)	0·014
Total bilirubin (μmol/l)	11 (6, 13)	16 (11, 34)	0·001
ALT (units/l)	42 (14, 110)	68 (44, 166)	0·007

Values are median (10th and 90th percentile). ALT, alanine aminotransferase. *Mann–Whitney U test

Table 3 Results of laboratory tests performed at the time of detection of recurrence

	Interferon group ($n = 9$)	Control group ($n = 13$)	P*
Albumin (g/l)	40 (36, 42)	37 (28, 39)	0·052
Total bilirubin (µmol/l)	12 (10, 17)	18 (10, 35)	0·044
ALT (units/l)	57 (26, 110)	70 (59, 160)	0·12

Values are median (10th and 90th percentile). ALT, alanine aminotransferase. *Mann–Whitney *U* test

control group. The cumulative survival rate was higher in the interferon group than in the control group ($P = 0{\cdot}041$, log rank test) (*Fig. 1*).

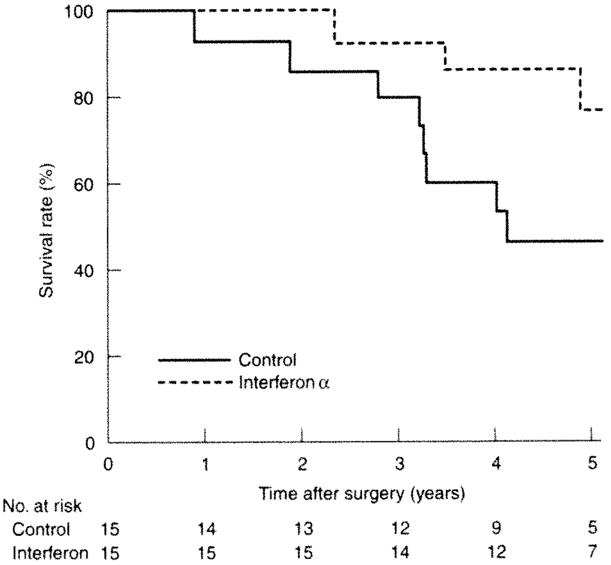

Fig. 1 Survival rates in the interferon and control groups. All censored patients were alive at the end of the trial. The survival rate was higher in the interferon group than in the control group ($P = 0{\cdot}041$, log rank test)

Discussion

In this study, the cumulative survival rate after resection of HCC was higher in the interferon group than in the control group. One of the nine patients with recurrence in the interferon group had multiple recurrent tumours, as did six of the 13 patients in the control group. Some recurrent tumours were intrahepatic metastases from a primary tumour that were not detected at operation, and others were carcinomas that seemed to have developed after operation. The prevalence of multicentric carcinogenesis increases during progression to active hepatitis and hepatic fibrosis[9,10]. Interferon suppresses the development of HCC by causing remission of active hepatitis and improvement in hepatic fibrosis in patients infected with HCV[3,5,11,12], although the risk of HCC seems to be smaller in complete responders than in biochemical responders[10]. Interferon may suppress multiple recurrences arising from multicentric carcinogenesis after the operation by such effects. Interferon-α has antiproliferative effects on a human hepatoma cell line[13]. Interferon can increase natural-killer cell activity and has antiangiogenic properties[14,15]. Ikeda *et al.*[16] reported that interferon-β prevents recurrence of HCC after treatment and suggested that interferon acts as an antitumour agent. Lai *et al.*[17] found that a combination of anticancer agents and interferon-α improved the survival rate of patients with advanced HCC. Anticancer effects of interferon may also explain the small number of recurrent tumours in the interferon group. The occurrence of multiple recurrent tumours has been identified as a risk factor for short survival time[18,19]; the lower incidence of such tumours in the interferon group in the current study may have contributed to the improved survival time.

The authors' previous study showed that recurrence was unlikely to occur more than 2 years after operation in the interferon group, but in this longer follow-up study HCC recurred in four patients in the interferon group. Three of these four patients still had HCV viraemia. These findings indicated that eradication of HCV is necessary to suppress carcinogenesis, and that carcinogenesis may occur even after the complete remission of chronic hepatitis C, as reported previously[3,5,10], although the risk is small.

Previous studies of survival after treatment for recurrence showed worsened liver function (including a high serum concentration of total bilirubin) to be a risk factor for short survival[18,19]. Serfaty *et al.*[20] have shown that risk factors for a short survival time in patients with HCV-related cirrhosis include a high concentration of total bilirubin and lack of interferon therapy. Interferon-α prevents worsening of compensated cirrhosis[5]. The laboratory results showed that liver function either improved or did not deteriorate in the interferon group. In the control group, the laboratory test results either did not change or worsened. At the detection of recurrence, the serum concentration of total bilirubin was significantly lower in the interferon group. With the progression of liver disease, the incidence of HCC increases[12]. Interferon may increase survival time by improving liver function and increasing the chance of radical treatment of recurrences.

Suppression of recurrence and improvement of liver function by postoperative interferon therapy may contribute to the improved outcome after resection of HCV-related HCC, although the number of patients in this study was too small for a firm conclusion to be reached. Patients with early-stage HCC and liver function good enough for liver resection and interferon therapy to be considered may be candidates for postoperative interferon therapy.

Acknowledgements

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Randomized clinical trial of the effectiveness of emergency day surgery against standard inpatient treatment

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Background: The aim of this study was to assess the feasibility of treating patients with minor and intermediate general surgical emergency conditions as day cases.

Methods: Emergency referrals for minor and intermediate general surgical conditions were assessed by a surgeon. Those fitting day-case criteria and requiring operation under general anaesthesia were randomized to receive standard inpatient care or day surgery. Patients in the latter group were booked on to day-case lists or gaps on inpatient elective lists for surgery within 48 h. The process was coordinated by an experienced theatre sister.

Results: One hundred patients were randomized. There was a reduction in the number of nights spent in hospital in the day-case group (median 0 *versus* 2 nights; $P < 0.001$). The median time from diagnosis to treatment was 1 day in both groups, although there was a small but significant delay in the day-case group ($P = 0.018$). There was no significant difference in postoperative outcome or patient and general practitioner satisfaction. The day-case option had no increased impact on primary care services but was associated with a significant saving of about £150 per patient ($P < 0.001$).

Conclusion: Certain general surgical emergencies may be managed as day cases with cost saving but without detriment to patient care.

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Introduction

Day-case surgery is widely accepted for many minor and intermediate elective surgical procedures[1]. The advantages of day-case surgery have not, as yet, been applied to the emergency situation. Many patients with minor and intermediate surgical emergencies would satisfy the health and social criteria for day-case surgery as proposed by the Royal College of Surgeons of England[2]. The majority of these patients are treated on daily priority-based emergency lists. In the large majority of cases this involves at least one postoperative night in hospital and frequently a preoperative overnight stay. For the patient the result is a prolonged period of starvation, uncertainty over the time of operation and a prolonged stay in hospital leading to increased disruption to work and social life.

The authors previously reported the results of a pilot scheme in which minor and intermediate surgical emergencies were given unplanned gaps on elective inpatient and day-case lists within 48 h or, failing this, on the next available emergency list for treatment as a day case[3]. This showed that many patients with suitable conditions could be treated successfully as a day case while maintaining high standards of patient satisfaction, and without an increase in perioperative complications or readmission rates. By means of a prospective randomized controlled trial this system has now been compared with the standard inpatient care that patients received before the introduction of the emergency day-case service. Delay from diagnosis to operation, the number of nights spent in hospital and the cost of treatment for each patient were chosen as major outcome measures for comparison.

Patients and methods

Emergency cases considered suitable for day-case treatment were patients with superficial abscesses, acutely painful hernias (excluding those causing strangulation or small

Table 1 Case mix in day-case and inpatient groups

	Day case	Inpatient
Abscess	46	47
Perianal	17	15
Pilonidal	10	13
Other	19	19
Hernia	2	1
Inguinal	1	1
Periumbilical	1	0
Thrombosed haemorrhoids	0	1
Other	2	1

bowel obstruction) and acutely thrombosed prolapsed haemorrhoids. All patients presenting as an emergency to the Whittington Hospital were assessed. Those meeting the admission criteria of the day-surgery unit (DSU) were invited to participate in the study. Patients allocated to the day-case arm of the study were placed on unplanned gaps that appeared on elective inpatient and day-case lists. The day-case assessment and booking process were coordinated by an experienced theatre sister. Patients allocated to the inpatient arm of the study were admitted and their names were placed on the Confidential Enquiry into Perioperative Deaths (CEPOD) emergency list. Preoperative assessment was dependent on age and co-morbidity but was identical between the two groups.

The number of nights spent in hospital and the delay from first presentation to operation was recorded for each patient. Follow-up was by outpatient appointment at 1–2 months using a standard pro forma that asked for information on postoperative pain, duration of analgesia use, use of primary care services after operation and patient satisfaction. Patients who did not attend for follow-up despite invitation were sent a postal questionnaire based on the outpatient pro forma. General practitioner (GP) questionnaires were sent out at the time of follow-up to assess both the postoperative use of primary care services and GP satisfaction. The two systems were also compared for mean cost per patient.

Statistical analysis

Bed-night usage and delay to surgery were compared using the Mann–Whitney *U* test, and the difference in cost was analysed with an unpaired *t* test. Pain scores were measured using a visual analogue scale and the two groups were compared with the *t* test. Rates of complications and patient and GP satisfaction were compared using Fisher's exact test. The duration of analgesia use and the impact on primary healthcare services were compared with the Mann–Whitney *U* test.

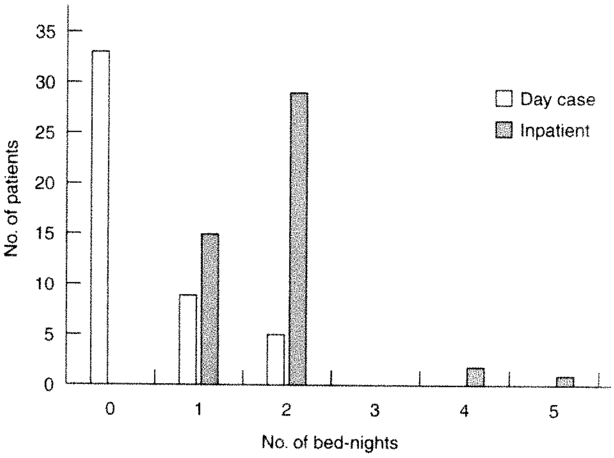

Fig. 1 Bed-night usage in day-case and inpatient groups

The sample size was determined using a power of 80 per cent to detect any differences between the day-case and inpatient groups as significant at the 5 per cent (two sided) level. The calculations were based on the difference between groups in the primary outcome measure of nights spent in hospital. On the assumption that the mean stay for day-case patients is 0·5 days and the common standard deviation is 0·8 days, a sample size of 92 patients (41 per group) would allow detection of a difference between the groups of 0·5 days or more. Analysis was performed using SPSS software (version 7.5.1, 1996; SPSS, Chicago, Illinois, USA).

Results

One hundred patients entered the study. The groups were well matched for age and case mix (*Table 1*). Some 94 patients were treated as randomized. Six patients did not undergo surgery, all of whom had superficial abscesses; four operations were cancelled by the surgeon because the abscess had ruptured in the intervening period (two day cases, two inpatients), one patient in the day-case group failed to attend for surgery and one inpatient left the ward without treatment.

Bed-night and delay to surgery analysis

Patients in the day-case group spent significantly fewer nights in hospital than their counterparts in the inpatient group ($P < 0{\cdot}001$). In the day-case group 33 of 47 patients were successfully treated as a day case, while the remaining 14 patients spent a total of 19 nights in hospital (mean 0·4 (95 per cent confidence interval (c.i.) 0·2 to 0·6) bed-nights per patient; median stay 0 (range 0–3) nights). The 47

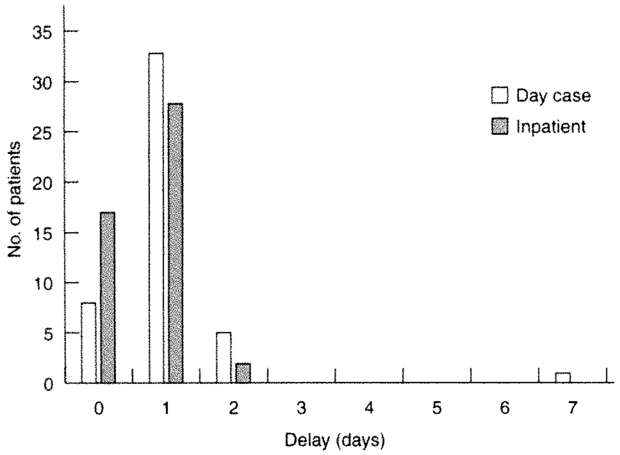

Fig. 2 Delay to treatment in day-case and inpatient groups

Table 2 Subgroup analysis of day-case group: comparison of wards

	Day-case unit	Inpatient ward
Mean(s.d.) age (years)	35·5(11·6)	42·5(16·8)
No. of men	15 of 32	9 of 15
Median (range) bed-nights	0 (0–2)	1 (0–2)
Median (range) delay (days)	1 (0–2)	1 (0–7)

Table 3 Visual analogue pain scores

	VAPS	
	Day case	Inpatient
24 h	4·8(2·3)	5·0(2·6)
Days 2–7	3·9(2·5)	3·7(2·1)
Days 8–14	1·8(1·7)	2·3(2·1)

Values are mean(s.d.). VAPS, visual analogue pain score. There were no significant differences between day-case and inpatient groups

patients treated as inpatients spent a total of 86 nights in hospital (mean 1·8 (95 per cent c.i. 1·6 to 2·1) bed-nights per patient; median stay 2 (range 1–5) nights) (*Fig. 1*). The difference in mean stay between inpatients and day cases was 1·4 (95 per cent c.i. 1·1 to 1·7) days.

The median delay from first presentation to surgery was 1 (range 0–7) day in the day-case group and 1 (range 0–2) day in the inpatient group. There was a small but significant delay in the time to surgery in the day-case group ($P = 0{\cdot}018$) (*Fig. 2*). One patient in the day-case group with a painful incarcerated inguinal hernia had the operation postponed for 6 days pending cardiology review, following the development of heart block before induction of anaesthesia. In the day-case group 41 of 47 patients were treated within 24 h of presentation. Subgroup analysis of the day-case group showed that the large majority of overnight stays in this group was in the subgroup of patients admitted to the inpatient wards. Thirty-two of 47 patients in the day-case group were treated on the DSU ward and the remaining 15 patients were treated on an inpatient ward. Twenty-nine of the 32 patients treated initially on the DSU were treated successfully as a day case compared with four of 15 treated initially on an inpatient ward. This resulted in a median bed-night stay of 0 (range 0–2) compared with 1 (range 0–2) night respectively ($P < 0{\cdot}001$). There was no significant difference between the subgroups in delay to surgery, and the age and case-mix were comparable (*Table 2*).

There were no readmissions within 30 days of operation in either group. Fourteen of 50 patients in the day-case group and 16 of 50 in the inpatient group attended the postoperative outpatient appointment. A further nine of the day-case patients and eight inpatients replied to the postal questionnaire. The visual analogue pain score (VAPS) was measured over three time periods: first 24 h, days 2–7 after surgery and days 8–14 after surgery. The VAPS was lower in the day-case group in two of the three time intervals but there was no significant difference between the groups (*Table 3*). There was no difference in duration of analgesia use (median 7 days in both groups). There were no significant complications in either group and no significant difference in the incidence of minor complications. There was no increased use of primary healthcare services by patients in the day-case group, in contrast to previous findings[4]. However, the number of visits to the district nurse was greater than would have been expected for elective day surgery owing to the number of superficial abscesses in the cohort. Patient satisfaction was high in both day-case and inpatient groups (96 *versus* 92 per cent respectively; *P* not significant).

Some 63 per cent of questionnaires sent to patients' GPs were returned. Three patients had left their GP practice since treatment, so 60 questionnaires were completed successfully. For patients in the day-case group 27 of 28 GPs expressed satisfaction with the treatment provided compared with 28 of 32 in the inpatient group (*P* not significant).

Comparison of cost

The cost of implementing the emergency day-surgery programme took into account the cost of employing the nurse coordinator. Although the data show evidence of skewness, this method is fairly robust to deviations from

Table 4 Cost of treatment

	Cost of treatment (£)	
	Day case	Inpatient
Mean(s.d.)	447(125)	594(145)
Median (range)	413 (350–779)	561 (394–1263)

normality and provides the necessary comparison of means as suggested by Thompson and Barber[5]. Mean cost per patient was £594 in the inpatient group and £447 in the day-case group. There was a significant saving ($P < 0{\cdot}001$) of £147 (95 per cent c.i. £92 to £202) per patient in the day-case group (*Table 4*).

Discussion

Day-case surgery has become the standard for an increasing range of surgical procedures in suitable patients. The range of cases suggested by the Audit Commission in 1990[6] has been expanded within many hospitals and this is reflected by suggestions from the British Association of Day Surgery in 1999[7]. Day surgery is popular among patient groups, health service providers and health service purchasers[2,6,8,9]. However, as yet, the advantages of this system have been applied only in the area of elective surgery.

Emergency surgery in the UK is carried out predominantly on emergency lists. Patients are treated in order of clinical priority. Operating at night has been discouraged following CEPOD reports[10]. As a result patients with minor and intermediate surgical emergencies can often wait 24 h or more for an operation. During this time they remain as inpatients, are intermittently starved and their expectations of time of surgery are frequently changed.

The emergency day-case scheme was set up to address this problem. Many patients with this type of surgical emergency fit the health and social criteria for elective day-case surgery. There is often spare capacity, albeit sporadic, on elective inpatient and day-case lists which could be used to treat these patients as day cases with a booked time. These gaps appeared as the result of late cancellations (e.g. lack of inpatient or intensive care beds for inpatient lists), shorter lists than expected (e.g. irresectable cancers) and failure of elective patients to arrive for surgery. An experienced theatre sister monitored the lists for these unplanned gaps and filled them with emergency patients. The DSU beds were used in the first instance and, when not available, inpatient beds were used. A pilot study entered 142 consecutive patients into this scheme; 70 per cent of these patients, who would otherwise have been treated as inpatients, were successfully treated as a day case. The results from the trial suggest that many of the problems associated with treating these conditions on emergency lists have been overcome by this scheme. Patients spent significantly fewer nights in hospital, had comparable pain scores, no excess complications, and the scheme had high patient and GP satisfaction. The high level of district nurse and practice nurse involvement compared with elective day surgery was a result of the case mix, predominantly superficial abscesses which required prolonged follow-up for dressing changes. However, there was no increased burden of work for the primary care teams in the day-case group compared with the emergency inpatient group. It was somewhat difficult to draw any conclusions from the questionnaires because the data were obtained from a mixture of outpatient interviews and postal questionnaires. Attendance at the outpatient follow-up was low (30 per cent overall) despite two invitations. The response to the postal questionnaire was also low (24 per cent). This can be explained partly by the nature of the conditions treated and the demographics of the population in the hospital's catchment area.

In the day-case group nearly one-third of patients were admitted, a higher proportion than would be expected for elective day surgery. The reasons for this are threefold. First, emergency day cases tend to get placed at the end of elective lists and as such are more likely to be cancelled in the event of an over-run list. Second, whereas all elective day cases are treated on the integrated DSU, 15 of 47 patients in the day-case group were treated on inpatient wards and it is this group that made up much of the failed discharge figures. Of the 32 patients treated on the DSU only three were not discharged on the same day compared with 11 of 15 patients in the day-case group who were treated on an inpatient ward. Third, the case mixes of elective and emergency day-cases are not comparable. Patients in the emergency setting are more likely to require admission because they are acutely unwell, and this can have both surgical and anaesthetic repercussions.

Increasingly, in the National Health Service, research findings must be balanced against the cost of their implementation. Perceived patient satisfaction is not sufficient. However, this study showed a significant saving of about £150 per patient when a suitable emergency patient was treated as a day case as opposed to receiving standard inpatient care.

In conclusion, it appears feasible to run an emergency day-surgery service for patients with minor and intermediate surgical emergencies. There are clear financial advantages to setting up such a service. However, this process requires consultant cooperation and an experienced nurse or manager to coordinate the process. The study also reaffirms the value of an integrated day-surgery unit[2].

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Peter Jones

Professor Peter Jones of Aberdeen recently donated a collection of *BJS* issues dating from April 1945 (volume 33) to December 2000 (volume 87) to The Academy of Medical Sciences and Technology, University of Khartoum. This was an impressive collection built up over many years. The Editors are pleased a useful home was found for these issues. We congratulate Peter Jones on his assiduous collection and for his kind donation to further surgical education in the Sudan.

The Editors

Randomized trial

Randomized clinical trial of Ligasure^{TM} *versus* conventional diathermy for day-case haemorrhoidectomy

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Background: Haemorrhoidectomy is frequently associated with postoperative pain and prolonged hospital stay. A new technique of haemorrhoidectomy using the Ligasure^{TM} device suited to day-case surgery is described. This technique was compared with conventional open diathermy haemorrhoidectomy.

Methods: Forty patients with grade III or IV haemorrhoids were randomized to Ligasure^{TM} (group 1) or conventional diathermy (group 2) haemorrhoidectomy. Operative details were recorded and patients recorded daily pain scores on a linear analogue scale. Follow-up was at 1, 3, 6 and 12 weeks to evaluate complications, return to normal activity, ongoing symptoms and patient satisfaction.

Results: Reduced intraoperative blood loss (median (range) 0 (0–5) ml *versus* 20 (12–22) ml; $P < 0{\cdot}001$) and a shorter operating time (10 (8–11) *versus* 20 (18–25) min; $P < 0{\cdot}001$) was observed in group 1 compared with group 2. More patients in group 1 were discharged on the day of operation (18 of 20 *versus* 11 of 20; $P < 0{\cdot}05$) and there was a trend towards lower postoperative pain scores on day 1 (group 1 median 5 (95 per cent confidence interval (c.i.) 2·6 to 6·8) *versus* group 2 7 (95 per cent c.i. 4·2 to 7·7); $P = 0{\cdot}36$). There was no difference between the two groups in the degree of patient satisfaction or number of postoperative complications.

Conclusion: Ligasure^{TM} diathermy may be used safely in the treatment of patients with grade III or IV haemorrhoids. It reduces intraoperative blood loss and operating time, and facilitates same-day discharge.

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Introduction

Haemorrhoidectomy is the treatment of choice for patients with symptomatic grade III and IV haemorrhoids[1]. Unfortunately, it may be accompanied by significant postoperative complications, including pain, bleeding and wound sepsis, which can result in a protracted period of recovery for the patient. Various modifications of the original Milligan–Morgan open technique[2] have been described, but none of these has shown consistent benefits over open haemorrhoidectomy in routine clinical use[3–5]. The introduction of circular stapling devices has renewed interest in haemorrhoidectomy with a promise of reduced postoperative pain[6–8]. Initial enthusiasm has been tempered by concerns about the long-term efficacy, inadvertent sphincter injury[9] and serious postoperative sepsis[10].

The Ligasure™ diathermy system allows accurate application of bipolar diathermy to vascular structures. It incorporates 'intelligent sensors' within the diathermy forceps, which ensure complete coagulation with minimal thermal spread and limited tissue charring. Theoretically, it is ideally suited to haemorrhoidectomy, where application results in a discrete line of coagulation that allows bloodless haemorrhoidal excision. The limited tissue injury may additionally reduce wound sepsis, facilitate healing and decrease postoperative pain.

In this study the technique of Ligasure™ haemorrhoidectomy is described and the results of a randomized controlled trial that compared open diathermy haemorrhoidectomy with Ligasure™ haemorrhoidectomy are presented.

Patients and methods

Patients and procedure

Between October 2000 and January 2001, 40 patients with symptomatic grade III or IV haemorrhoids were recruited

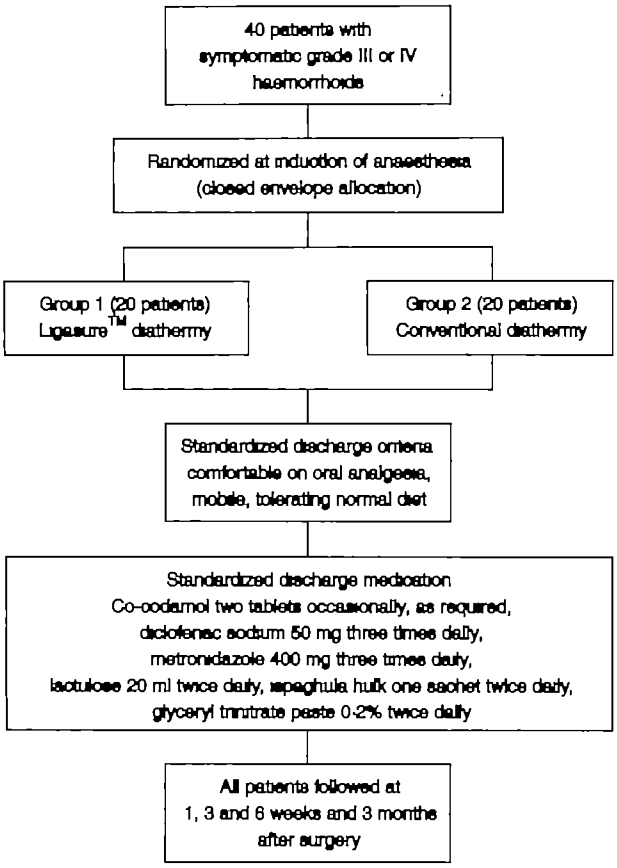
40 patients with
symptomatic grade III or IV
haemorrhoids
Randomized at induction of anaesthesia
(closed envelope allocation)
Group 1 (20 patients)
Ligasure™ diathermy
Group 2 (20 patients)
Conventional diathermy
Standardized discharge criteria
comfortable on oral analgesia,
mobile, tolerating normal diet
Standardized discharge medication
Co-codamol two tablets occasionally, as required,
diclofenac sodium 50 mg three times daily,
metronidazole 400 mg three times daily,
lactulose 20 ml twice daily, ispaghula husk one sachet twice daily,
glyceryl trinitrate paste 0·2% twice daily
All patients followed at
1, 3 and 6 weeks and 3 months
after surgery

Fig. 1 Schematic profile of randomized controlled trial comparing Ligasure™ diathermy against conventional open diathermy in the treatment of symptomatic grade III and IV haemorrhoids

to the trial according to the profile in *Fig. 1*. Approval of the local ethics committee had been obtained. Exclusion criteria included the use of regular anticoagulants, immunosuppressants or analgesics, patients with American Society of Anesthesiologists grade III and IV, pregnancy, and the inability to give written informed consent. Primary endpoints included technical ease (operating time and blood loss) and procedure-related complications (pain and haemorrhage). Secondary endpoints included length of hospital stay, time to first bowel motion, return to normal activity and faecal incontinence score. Patient demographics, symptoms, details of previous treatments and preoperative faecal incontinence scores[11] were recorded. Randomization was to either group 1 (Ligasure™) or group 2 (conventional haemorrhoidectomy) by closed envelope allocation.

Under standardized general anaesthesia, patients were placed in the lithotomy position. A mixture of bupivacaine 0·5 per cent and adrenaline 1 : 200 000 was infiltrated into the subcutaneous and submucosal planes to elevate the haemorrhoidal pedicles from the underlying anal sphincter muscle. Ligasure™ haemorrhoidectomy was performed by applying the diathermy forceps across the haemorrhoid, together with any associated skin tag. Completion of coagulation was signalled by the feedback sensors, and haemorrhoidal tissue was excised along the line of coagulum. Repeated applications of the forceps were performed, as necessary, for complete haemorrhoidal excision, and a haemostatic sponge was inserted into the anal canal. Conventional haemorrhoidectomy was performed by submucosal dissection of the haemorrhoidal tissue from the internal sphincter using standard monopolar diathermy. Pedicles were transfixed, taking care to avoid incorporation of the underlying sphincter; haemorrhoids were excised and the wounds left open with a haemostatic sponge in the anal canal.

The position and number of haemorrhoids excised, together with associated skin tags, were recorded for both groups in addition to the operating time, blood loss and any technical complications. In 12 patients from each group, the excised haemorrhoid was sent for histological examination.

Postoperative care and follow-up

Morphine (10 mg intramuscular) and co-codamol (two tablets) were administered for pain control, and metaclopromide (10 mg) was used for antiemesis – all, as required. Pain scores, analgesic requirements, complications and length of stay were recorded. Patients were assessed for discharge on the evening of the operation by a surgical registrar blinded to the result of randomization. Patients were allowed home when comfortable on oral analgesics, fully mobile and tolerating a normal diet. Discharge medication included diclofenac sodium (50 mg three times daily), co-codamol (two tablets occasionally, as required), ispaghula husk (one sachet twice daily), lactulose (20 ml twice daily), metronidazole (400 mg three times daily) and glyceryl trinitrate paste (0·2 per cent topically twice daily). Pain scores were recorded for 7 days after operation using a ten-point linear analogue scale.

Follow-up was performed at 1, 3 and 6 weeks by colorectal nurse specialists blinded to the result of randomization. Pain scores, analgesic usage, time to first bowel motion, return to normal activities, and complications were noted. Faecal incontinence scores, symptom control and overall patient satisfaction were assessed at 12 weeks' follow-up.

Table 1 Characteristics of patients randomized to group 1 (Ligasure™) or group 2 (diathermy) haemorrhoidectomy

	Group 1 (*n* = 20)	Group 2 (*n* = 20)
Mean (range) age (years)	48 (26–75)	43 (33–77)
Sex ratio (M : F)	11 : 9	10 : 10
Symptoms (months)		
< 12	4	2
12–24	3	2
> 24	13	16
Grade		
III	16	16
IV	4	4
Previous treatment*	11 (1)	10 (1)

*Values in parentheses are the numbers of patients undergoing surgery

Table 2 Operative details of patients undergoing Ligasure™ (group 1) or conventional open (group 2) diathermy

	Group 1 (*n* = 20)	Group 2 (*n* = 20)	*P*
No. of haemorrhoids resected			n.s.*
1	0	0	
2	6	4	
3	12	14	
4	2	2	
No. of skin tags excised			n.s.*
1	3	2	
2	2	1	
3	4	4	
4	4	4	
Median blood loss (ml)	0 (0·5, 7·1)	20 (14·9, 35·0)	< 0·001†
Median operating time (min)	10 (8·8, 10·7)	20 (18·7, 24·4)	< 0·001†

Values in parentheses are 95 per cent confidence intervals. n.s., Not significant. *Fisher's exact test, †Mann–Whitney *U* test

Statistical analysis

Twenty patients were treated in each group to detect a difference of one standard deviation in mean operating time and blood loss, with an 80 per cent power at a 5 per cent level of significance. All data analysis was performed using the Statistical Package for the Social Sciences version 9·0 (SPSS, Chicago, Illinois, USA). Continuous variables were compared using the Mann–Whitney *U* test and categorical variables using the χ^2 or Fisher's exact test.

Results

Preoperative

Forty patients were randomized to the trial. Adequacy of randomization was demonstrated by the similarity in patient characteristics in both groups (*Table 1*). No protocol violations were recorded throughout the study.

Operative

The extent of haemorrhoidal disease was similar between the two groups, with a median of three haemorrhoids and three skin tags excised (*Table 2*). Statistically significant differences were observed in the technical ease related to the two procedures as assessed by operating time and intraoperative blood loss. Median (range) operating time was lower in group 1 than in group 2 (10 (8–11) min (95 per cent confidence interval (c.i.) 8·8 to 10·7 min) *versus* 20 (18–25) min (95 per cent c.i. 18·7 to 24·4 min); $P < 0.001$), while blood loss was virtually eliminated in group 1 compared with a small but significant blood loss in group 2 patients (median (range) 0 (0–5) ml (95 per cent c.i. 0·5 to 7·1 ml) *versus* 20 (12–22) ml (95 per cent c.i. 14·9 to 35 ml); $P < 0.001$).

Postoperative

Although the majority of patients in both groups were treated as day cases, significantly more patients were discharged on the day of operation in group 1 compared with group 2 (18 of 20 *versus* 11 of 20 respectively; $P < 0.05$) (*Fig. 2*). Analysis of the postoperative pain scores revealed a trend towards less discomfort on day 1 in group 1 patients, although this was not statistically significant (median (range) 5 (1–9) (95 per cent c.i. 2·6 to 6·8) *versus* 7 (4–9) (95 per cent c.i. 4·2 to 7·7); $P = 0.36$). Subsequently, the recorded pain scores of the two groups converged, with a gradual reduction to day 7. There was no difference in oral analgesic usage between the two groups.

Three complications were observed in group 1 and two in group 2. One patient in each group experienced reactive haemorrhage requiring hospital admission. One patient in each group complained of protracted pain resulting from the development of an anal fissure. Both responded to treatment with stool softeners and topical glyceryl trinitrate paste. A single patient in group 1 experienced postoperative urinary retention which responded to temporary bladder catheterization. No significant difference was observed between the groups in the median (range) time to first bowel motion (2 (1–5) days for group 1 *versus* 2 (1–4) days for group 2) or return to normal activity at 3 weeks' follow-up (group 1, 17 of 20; group 2, 15 of 20).

At 3 months' follow-up, 19 patients in group 1 were free from haemorrhoidal symptoms, compared with 16 in group

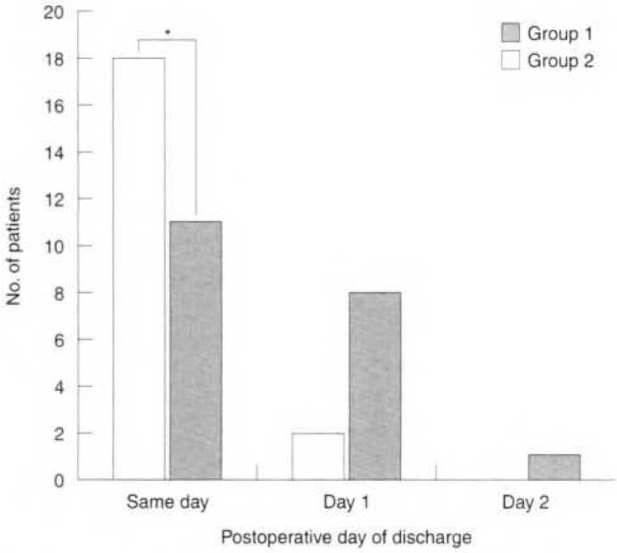

Fig. 2 Postoperative day of discharge following haemorrhoidectomy. $^*P < 0.05$ (Fisher's exact test)

2. One patient in group 1 had continuing discomfort, while two in group 2 had continuing bleeding and two had discomfort and bleeding. Assessment of faecal incontinence scores showed a minor increase compared with preoperative levels in three (group 1) and five (group 2) patients. There were no episodes of major faecal incontinence indicative of significant anal sphincter injury. However, histological analysis showed evidence of internal anal sphincter muscle sampling in six of 12 samples in group 1 and in seven of 12 samples in group 2.

Assessment of patient satisfaction at 3 months showed that ten of the 20 patients in group 1 and nine of the 20 in group 2 felt that their experience of haemorrhoidectomy was better than expected, while six and five patients respectively reported their experience to have been the same as anticipated. Only four patients in group 1 and six in group 2 described their experience as worse than expected, all due to a greater than expected degree of postoperative discomfort.

Discussion

The Ligasure™ diathermy system offers an excellent method for achieving bloodless dissection of vascular tissues. The combination of localized coagulation with minimal collateral thermal spread makes it an ideal instrument for diathermy haemorrhoidectomy.

This study shows that the new technique offers several advantages over conventional open diathermy haemorrhoidectomy. Technically, it is simple, easy to learn and quick to apply. In addition, more patients can be discharged on the same day as the operation compared with conventional haemorrhoidectomy. That only 11 of 20 patients in the conventional group went home on the same day – a lower proportion than reported by others – may reflect the strict discharge criteria used in this trial. Strenuous efforts were taken to avoid the introduction of biases into the study. In particular, patients were blinded throughout the study period and the discharge assessor was blinded to the result of randomization. The authors therefore believe that the observed differences in postoperative stay are real and are probably due to an early reduction in patient discomfort.

An area of concern with any technique for haemorrhoidectomy is the potential for inadvertent anal sphincter damage. However, with the use of adequate tissue retraction and submucosal infiltration, the haemorrhoidal plexuses can be readily elevated off the underlying anal sphincter, allowing safe application of the diathermy forceps. Although in six of 12 patients in group 1 there was evidence of superficial internal anal sphincter sampling on histological examination, this was always superficial in nature and similar to histological findings after conventional haemorrhoidectomy. Certainly, no case of significant anal sphincter injury was observed, nor was there any evidence of major sphincter injury as assessed by faecal incontinence scoring. Many of the problems relating to incontinence following haemorrhoidectomy may be attributable to sphincter stretching during the operative procedure. This component of sphincter injury is minimized by the Ligasure™ technique.

In this study there have been no unexpected complications. In contrast, circular stapling haemorrhoidectomy has been followed by reports of serious complications including pelvic sepsis[9] and anastomotic stenosis[12]. Furthermore, failure to deal with external haemorrhoidal components and skin tags can lead to an unsatisfactory cosmetic result in some 20–40 per cent of patients treated with circular stapling[13]. Although residual skin tags are believed to shrivel over time, this will be verified only with further long-term follow-up. This problem is avoided with the use of Ligasure™ diathermy, which can deal effectively with both internal and external haemorrhoidal components, giving excellent cosmesis.

There may be a cost benefit associated with this new technique. Ligasure™ diathermy adds a minimal additional cost to the surgical procedure (approximately £85 per disposable diathermy forceps), which is likely to be offset by the reduction in postoperative stay and compares favourably with the additional costs involved with other haemorrhoidectomy techniques.

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Original article

Comparison of magnetic resonance cholangiography and percutaneous transhepatic cholangiography in the evaluation of bile duct strictures after cholecystectomy

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Background: Percutaneous transhepatic cholangiography (PTC) has been the preferred investigation to delineate the anatomy of the biliary tract in a patient with a bile duct stricture after cholecystectomy. Recently magnetic resonance cholangiography (MRC) has been described to evaluate the obstructed biliary tract. This paper reports a comparison of MRC with PTC in evaluating patients with an iatrogenic bile duct stricture.

Methods: This was a prospective study of 26 patients who had surgery for a bile duct stricture after cholecystectomy. Before operation all patients underwent both MRC and PTC, the results of which were compared with the intraoperative findings.

Results: Both PTC and MRC were comparable with regard to image quality, detection of intrahepatic bile duct dilatation, assessment of the level of injury and detection of abnormalities such as intraduct calculi, cholangitic liver abscesses and atrophy of liver lobes. MRC provided additional information in four patients, including detection of associated fluid collections ($n = 3$) and portal hypertension ($n = 1$). In eight patients more than one puncture had to be performed during PTC to delineate the complete anatomy.

Conclusion: MRC is an accurate and non-invasive imaging procedure for preoperative evaluation of patients with a bile duct injury after cholecystectomy, and is capable of providing additional information which may not be available with PTC.

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Introduction

Successful surgical repair of a bile duct stricture necessitates a complete cholangiographic assessment of the biliary tree to ensure that all hepatic segments would be drained adequately by the proposed bilioenteric anastomosis[1]. Percutaneous transhepatic cholangiography (PTC) has been the preferred investigation for this purpose. Evaluation by endoscopic retrograde cholangiography is limited by the fact that it demonstrates only the lower end of the obstruction and fails to delineate the proximal biliary tract. Recently, magnetic resonance cholangiography (MRC) has been used to visualize obstructed bile ducts. MRC has been studied most thoroughly in patients with choledocholithiasis[2–4]. Although it is sensitive in localizing other causes of biliary obstruction, its role in the preoperative evaluation of bile duct injuries has not been studied adequately. This prospective analysis compared the results of MRC and PTC in patients with iatrogenic bile duct strictures being considered for surgical repair.

Patients and methods

Between June 1998 and December 2000, 26 patients who needed biliary–enteric bypass for bile duct injury following cholecystectomy were evaluated prospectively by both MRC and PTC. All patients underwent preliminary abdominal ultrasonography.

Magnetic resonance cholangiography

MRC was performed no more than 72 h before surgery using a 1-T scanner (Siemens Medical Systems, Erlangen, Germany). All sequences were performed during breathholding. After localized imaging, heavily T2-weighted pulse sequences were obtained in coronal and transverse planes. Two three-dimensional turbo spin echo techniques were acquired whenever possible: a single-shot rapid acquisition with relaxation enhancement technique and a further addition of a half-Fourier turbo spin sequence during a breath-hold for 18 s. The total room time was less than 10 min per patient. No contrast or antiperistaltic drugs were used.

Percutaneous transhepatic cholangiography

PTC was performed under ultrasonographic guidance, within 24 h of surgery under antibiotic cover. The right-sided bile duct system was punctured. Additional punctures were performed if it was not possible to obtain complete imaging of all ducts, even after rotation and table tilt. The investigation was solely diagnostic.

Analysis

The images obtained by both MRC and PTC were interpreted separately by a blinded radiologist and surgeon. The findings recorded included the presence of biliary dilatation, the level of injury, any bile collections, the presence of calculi, strictures and abscesses in the intrahepatic ducts, atrophy–hypertrophy of the liver lobes, and evidence of anastomotic stenosis in patients with a previous biliary–enteric anastomosis.

All patients underwent Roux-en-Y hepaticojejunostomy. The findings of the radiological investigations were corroborated with the operative findings.

Results

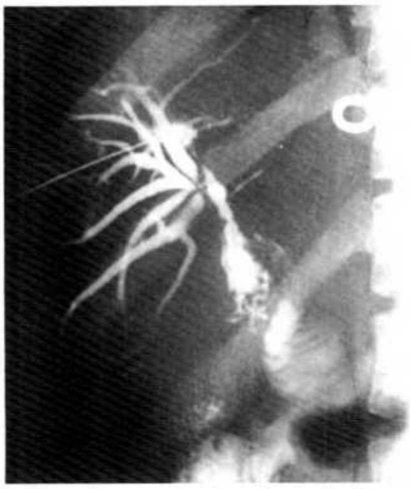
The patients included 19 women and seven men with a mean age of 35 (range 17–60) years. Bile duct injury occurred during laparoscopic cholecystectomy in 12 patients, while in 14 it followed open cholecystectomy. Four patients had already had a hepaticojejunostomy 3–14 months before presentation, which had stenosed. Symptoms in these 26 patients included jaundice ($n = 20$), recurrent cholangitis ($n = 11$), pruritus ($n = 10$) and an external biliary fistula ($n = 1$). One patient was known to have portal hypertension and had received endoscopic sclerotherapy to obliterate the oesophageal varices.

Good images were obtained from both MRC and PTC in all the patients. Motion-related artefacts or artefacts due to metallic clips were not encountered on MRC. In 18 patients PTC demonstrated the entire biliary tract from a single puncture of the right-sided duct system. In the remaining eight patients more than one puncture was necessary to delineate the biliary anatomy; five of these had Bismuth type IV strictures and needed puncture of the left bile duct sytem. Three patients had non-dilated ducts, and multiple punctures of the right-sided duct system were required to opacify the biliary tree. Three patients developed cholangitis after PTC that necessitated parenteral antibiotics for 5 days. No patient had bleeding or reaction to the contrast agent, and four patients needed analgesics for pain relief.

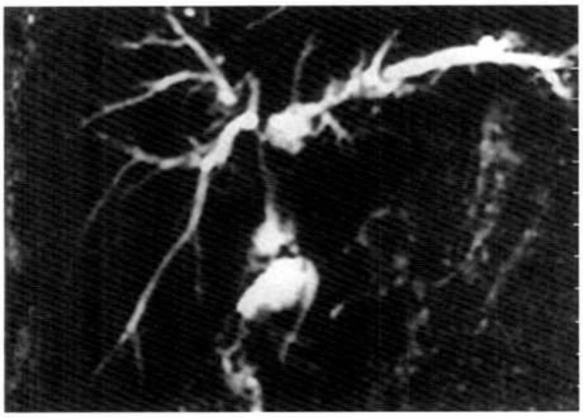
PTC and MRC were equally reliable and comparable in assessing biliary dilatation. Five patients had a Bismuth type I biliary stricture, nine had a type II, seven had a type III and five had a type IV stricture. The findings on PTC and MRC were accurate in this regard too but, as already mentioned, PTC initially showed only the right-sided duct system in patients with a Bismuth type IV stricture (*Fig. 1a*). In these patients the left system could not be opacified by the right-sided puncture owing to the hilar disconnection. In contrast, MRC in these five patients showed the duct systems on both the right and left sides of the liver (*Fig. 1b*). Both PTC and MRC accurately detected the stricture in the four patients with a biliary–enteric anastomosis performed previously for bile duct stricture after cholecystectomy. Atrophy of the right lobe of the liver with compensatory hypertrophy of the left lobe was present in one patient and was diagnosed by both PTC and MRC. In two patients calculi in the intrahepatic ducts ranging in size from 5 to 10 mm were revealed by both imaging methods. Cholangitic abscesses in the liver were found in two patients and were equally well shown by PTC and MRC (*Figs 2* and *3*). Three patients had associated bile collections (in the gallbladder fossa in two and the hepatoduodenal ligament area in one), which were seen only on MRC. Percutaneous drainage was performed in these patients. One patient was known to have portal hypertension but another with no symptoms or signs of portal hypertension had the diagnosis revealed on magnetic resonance imaging by the presence of splenomegaly and pericholedochal collaterals. Endoscopy was performed in this patient and revealed grade II oesophageal varices. Overall, therefore, in four patients MRC provided additional information that was not available on PTC.

Discussion

MRC was introduced in the early 1990s[5] and since then its application in the evaluation of the obstructed bilary tract has expanded rapidly. Few studies have been dedicated to patients with bile duct stricture after cholecystectomy[6]. PTC has so far been the 'gold standard' investigative technique for evaluating patients with a bile duct stricture. The present study suggests that MRC is superior to PTC, being non-invasive, more 'patient friendly' and also capable



a Percutaneous transhepatic cholangiogram



b Magnetic resonance cholangiogram

Fig. 1 **a** Percutaneous transhepatic cholangiography in a patient with a Bismuth type IV stricture opacifying only the right-sided hepatic ducts. **b** Magnetic resonance cholangiography in the same patient showing the bile duct system on both sides of the liver

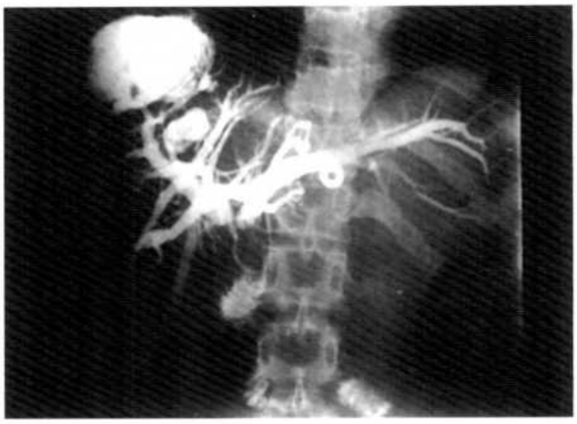


Fig. 2 Percutaneous transhepatic cholangiography showing multiple cholangitic liver abscesses

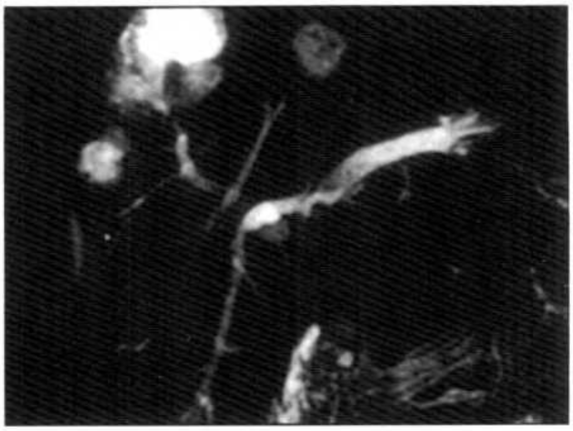


Fig. 3 Cholangitic liver abscesses seen on magnetic resonance cholangiography

of providing additional information, as was seen in four patients. MRC detected a bile collection in three patients and unsuspected portal hypertension in one. MRC was superior to PTC in patients with a Bismuth type IV stricture, since at least two punctures were necessary to get a complete evaluation of ductal anatomy owing to hilar discontinuity. Patients with high bile duct strictures and isolation of the right and left hepatic ducts, patients with undilated ducts and those with biliary obstruction at multiple levels are best suited for MRC as a single investigation provides the entire examination. Biliary ducts that have been excluded from the main duct system owing to injury can be missed during PTC and, if not incorporated in the biliary–enteric anastomosis, may result in the development of cholangitis. These 'isolated' ducts are seen easily on MRC because visualization is not dependent on the flow of contrast material. The stationary fluid in the bile ducts serves as an intrinsic contrast medium. In addition, MRC has been reported to provide better visualization of the peripheral biliary tree than direct cholangiography[7].

Yeh *et al.*[6] recently published their experience with MRC in four patients with bile duct injury after laparoscopic cholecystectomy, and found it to be useful and accurate. Pavone *et al.*[8] reported their experience of MRC in 24 patients with biliary–enteric anastomoses, 22 of whom had had a hepaticojejunostomy for iatrogenic bile duct stricture. As in the present study, MRC was sensitive in the detection of bile duct irregularities, anastomotic strictures and intrahepatic calculi. MRC has also been used to evaluate the biliary tract after liver transplantation, with 100 per cent reported sensitivity and specificity in the detection of duct-to-duct and biliary–enteric anastomotic strictures[9]. In a prospective evaluation of 15 patients with benign bile duct strictures of various aetiologies MRC correctly identified the presence, location and cause of the stricture in all patients[10]. Coakley *et al.*[11] reported a preliminary experience with MRC in evaluating 17 patients with complex biliary disorders after cholecystectomy and found it to be an accurate, non-invasive modality for assessing biliary occlusion, peribiliary lesions, non-specific biliary dilatation and bile duct stones. MRC can also detect anatomical variants such as low and right-sided insertion of the cystic duct, parallel course of the cystic duct with the hepatic duct and presence of an aberrant right hepatic duct[12].

MRC has the advantage that in a single study it can provide cross-sectional images of the entire liver. In addition, magnetic resonance angiography can be performed at the same time to assess any vascular injury. Thus a single study can provide information that otherwise might need multiple tests. MRC does not need any preparation, nor use of a contrast agent, and it can be performed safely in sick patients who have cholangitis or a deranged coagulation profile. Since PTC can cause complications such as cholangitis, bile leaks and even haemorrhage, it is always performed just before surgery. Three patients in the present study needed antibiotics after PTC and four received analgesics. MRC can be performed at any time before operation and so gives a greater flexibility for the surgeon in planning the surgical procedure.

The main limitation of MRC is that it is only diagnostic and has no therapeutic potential; moreover it is comparatively more expensive than PTC and is less widely available. As MRC visualizes the bile ducts in their physiological state, the bile duct segment immediately distal to a tight stricture may be collapsed and appears as a part of the stricture. Therefore, in some cases a stricture may appear longer than it really is. This is not a problem with bile duct strictures after cholecystectomy, as in this case the proximal extent of the narrowing is more important.

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Original article

Uptake of Lipiodol™–cytotoxic conjugates by hepatoblastoma cells

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Background: Improvements in the management of children with hepatoblastoma have followed advances made in cytotoxic agents and treatment regimens. The aim of this study was to quantify the effect of Lipiodol™, an iodinated poppy-seed oil, on the uptake of anthracyclic cytotoxic conjugates by hepatoblastoma cells in culture.

Methods: Monolayer cultures of (1) a hepatoblastoma cell line generated from freshly explanted tumour tissue, (2) an immortal hepatoblastoma cell line (C3a) and (3) a human hepatocyte cell line were exposed to doxorubicin 10 µg/ml with or without 2 per cent Lipiodol™ for 1–72 h. The fluorescence intensity in the treated cells, which correlates with intracellular doxorubicin concentration, was measured by confocal laser scanning microscopy. Cytotoxicity was assessed by trypan blue exclusion and electron microscopy.

Results: Doxorubicin accumulated in the nucleus and cytoplasm of all the cell lines. With Lipiodol™, the mean fluorescence intensity of intracellular doxorubicin was increased for up to 48 h in both hepatoblastoma lines, but not in the hepatocyte cell line. Lipiodol™ increased the uptake and intracellular concentration of doxorubicin in the hepatoblastoma cells in culture. Lipiodol™ also enhanced the cytotoxicity of doxorubicin on the cultured hepatoblastoma cells.

Conclusion: Lipiodol™ significantly enhanced the uptake of doxorubicin by hepatoblastoma cells in culture. Lipiodol™–doxorubicin targeted treatment of hepatoblastoma may improve the intracellular uptake and hence cytotoxicity of doxorubicin *in vivo*, enabling a reduction in the total dose administered and side-effects.

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Introduction

The prognosis and resection rate of hepatoblastoma has improved since the introduction of neoadjuvant chemotherapy. The 5-year cumulative probability of survival in patients with hepatoblastoma treated with intent to cure is 67 per cent[1–4]. The uptake of Lipiodol™ (Laboratoire Guernet, Roissy de Gaulle, France), an iodinated poppy-seed oil, by hepatocellular carcinoma cells *in vitro* and *in vivo* has been utilized as a means of targeting chemotherapeutic and radiotherapeutic agents, particularly in patients with advanced or irresectable hepatocellular carcinoma[3,5,6]. Lipiodol™ is taken up and selectively retained by hepatocellular carcinoma cells for prolonged periods compared with normal cells and may deliver cytotoxic agents at a higher concentration and for longer periods than would otherwise be achievable[3,6,7]. The mechanism of intracellular delivery of different chemotherapy agents bonded to Lipiodol™ remains unclear. The uptake of Lipiodol™ into liver cells is by pinocytosis as intracellular vesicles[3]. Ogita *et al.*[8] in 1987 treated two infants with irresectable hepatoblastoma by intra-arterial injection of doxorubicin, cisplatin and 5-fluorouracil dispersed in Lipiodol™. Others have also used this to treat children with 'irresectable' hepatoblastoma, with a marked reduction in tumour size allowing safe resection without marked chemotherapy-induced toxicity[9–11].

The aim of this study was to evaluate the effect of Lipiodol™ on the uptake and cytotoxicity of doxorubicin by hepatoblastoma and normal liver cell lines by means of confocal laser scanning microscopy (CLSM). Highly fluorescent molecules such as the anthracyclines have been observed to exhibit distinct patterns of intracellular accumulation and localization[12,13]. Doxorubicin and daunorubicin have been localized in the nucleus of many cultured cells by CLSM[14,15]. The advantages of the technique over conventional fluorescence microscopy include its greater vertical and lateral resolution, and the elimination of epifluorescence, including out-of-focus blur[16].

Materials and methods

The cell lines used in this study were a locally established hepatoblastoma cell line (HepTow), an immortal hepatoblastoma cell line (C3a) and a locally established normal hepatocyte cell line as control. A 1 × 1-cm block of tumour tissue was taken from a 4 × 4-cm hepatoblastoma that was surgically removed from the right hepatic lobe of a 3-year-old girl with a mixed fetal and mesenchymal hepatoblastoma. The tissue was minced and homogenized with 0·01 per cent collagenase and 0·05 per cent trypsin. Dulbecco's Modified Eagle's Medium (DMEM; Sigma Chemicals, Poole, UK) containing 20 per cent fetal calf serum (FCS), penicillin 100 units/ml and streptomycin 1 mg/ml was added to the homogenate, which was then filtered through a 60-µm filter and centrifuged at 300*g* for 10 min to achieve maximum cell yield. The cells were resuspended in DMEM and recentrifuged at 90*g* for 7 min for a more selective hepatoblastoma cell yield. The hepatoblastoma cell line C3a was obtained from the American Type Culture Collection, Rockville, Maryland, USA.

The hepatoblastoma cell lines were maintained as a monolayer in DMEM with 20 per cent FCS, penicillin 100 units/ml and streptomycin 100 µg/ml in chamber slides in an incubator maintained at 37°C and pregassed with 5 per cent carbon dioxide in air.

The human hepatocytes were cultured in a thin film of Biomatrix™ (TCS Biological, Buckingham, UK) in a 25-mm^2 culture flask with DMEM, hepatocyte growth factor 10 ng/ml and 10 per cent FCS, supplemented with penicillin 100 units/ml and streptomycin 100 µg/ml. The cells were then cultured in an incubator that was pregassed with 5 per cent carbon dioxide in air and maintained at 37°C. The cells were dispensed into 24-chamber slides at 1–2 million cells per ml and were then allowed to grow to a point of subconfluence.

The experimental groups (in triplicate) were as follows: (1) untreated group; (2) 2 per cent Lipiodol™ with DMEM; (3) doxorubicin 10 µg/ml with DMEM; and (4) 2 per cent Lipiodol™ admixed with doxorubicin 10 µg/ml with DMEM.

CLSM was performed with a Biorad MRC 600 confocal microscope (Bio-Rad, Hemel Hempstead, UK). Specimens were viewed in fluorescence and twin confocal transmission modes, at an excitation wavelength of 568 nm. Predetermined optical settings for confocal aperture, gain, black-level and illumination intensity were used for image acquisition throughout. Single optical slices of approximately 2 µm were collected over an average of five scans to reduce random electrical noise, using the Kalman filter function. Fluorescence was quantified by a computerized mean of five observations of pixel intensity distribution.

The four experimental groups were also analysed by light and electron microscopy. A trypan blue exclusion technique was used to assess the percentage of non-viable cells and hence the cytotoxic effect of the various treatments on each cell line.

Statistical analysis

Data on fluorescence intensity in the treated cells were analysed using the SPSS for Windows programme (SPSS UK, Birmingham, UK). Results were expressed as mean fluorescence integration of five observations. Fluorescence intensity was analysed using the unpaired *t* test. Cytotoxicity was analysed by analysis of variance. $P < 0.05$ was considered significant.

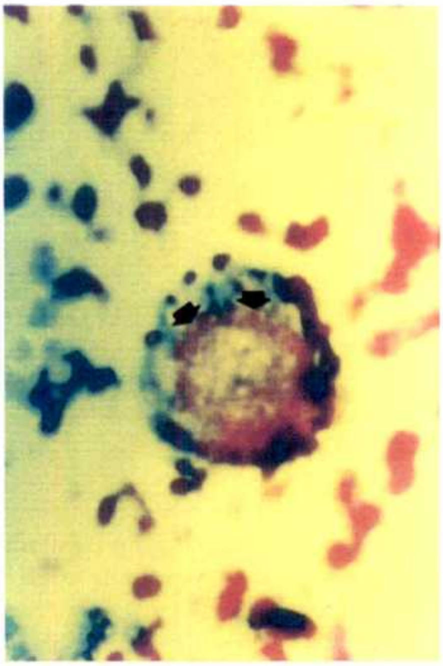

Fig. 1 Fluorescence in a hepatoblastoma cell exposed to doxorubicin, showing intranuclear fluorescence (arrows)

Results

Light and electron microscopy

HepTow and C3a cells were characterized by a distinct blue stain when stained with Carazzi's haematoxylin. There was brown staining of the cytoplasm and the nuclei of cells exposed to Lipiodol™ when the cells were stained with 2·5 per cent silver nitrate. Electron microscopy revealed HepTow cells to be undifferentiated, large and variable in size and shape, without gap junctions and features of hepatocyte differentiation. The cytoplasm contained a well developed secretory apparatus and scattered lipid droplets, which were markedly increased in the cells cultured with Lipiodol™, and occasional clusters of glycogen particles. The cell surface had prominent microvilli. The nuclei were hyperpig-mented, consistent with a malignant epithelial liver tumour.

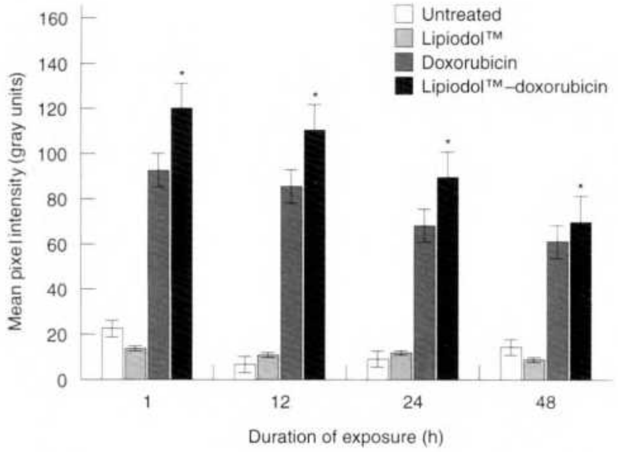

Fig. 2 Fluorescence in untreated hepatoblastoma cells and cells treated with Lipiodol™ alone, doxorubicin alone or Lipiodol™–doxorubicin. Values are mean(s.d.). $^*P < 0{\cdot}05$ *versus* doxorubicin (paired *t* test)

Confocal fluorescense intensity

The fluorescence intensity of doxorubicin in hepatoblastoma (C3a and HepTow) cells was mainly nuclear at 1 h (*Fig. 1*). Significantly enhanced fluorescence was noted in the cells that were exposed to both doxorubicin and Lipiodol™ ($P < 0{\cdot}05$) compared with those that were exposed to doxorubicin alone. These differences were assessed quantitatively by measuring the mean pixel intensity distribution in the cells after different times of exposure (*Figs 2* and *3*). The human hepatocyte fluorescence was lower than that in tumour cell lines and the fluorescence decreased more rapidly, implying that human hepatocytes were able to dispose of the anthracyclines more rapidly than the tumour cell lines.

After exposure for 48 h, the fluorescence in the hepatoblastoma cells treated with Lipiodol™–doxorubicin decreased, largely as a result of cellular destruction and extravasation of doxorubicin. This was evident when the background fluorescence in the culture increased after 48 h.

Light microscopy, trypan blue exclusion and electron microscopy revealed that the addition of Lipiodol™ to doxorubicin increased the sensitivity and cytotoxicity of the tumour cell lines to doxorubicin (*Fig. 4*).

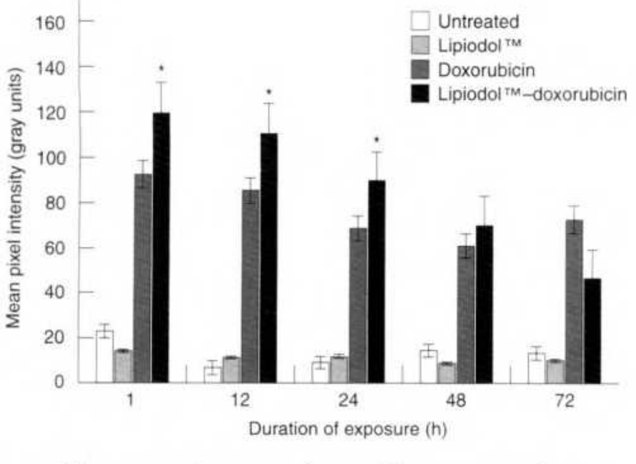

Fig. 3 Fluorescence in untreated normal hepatocytes and hepatocytes treated with Lipiodol™ alone, doxorubicin alone or Lipiodol™–doxorubicin. Values are mean(s.d.). $^*P < 0{\cdot}05$ *versus* doxorubicin (paired *t* test)

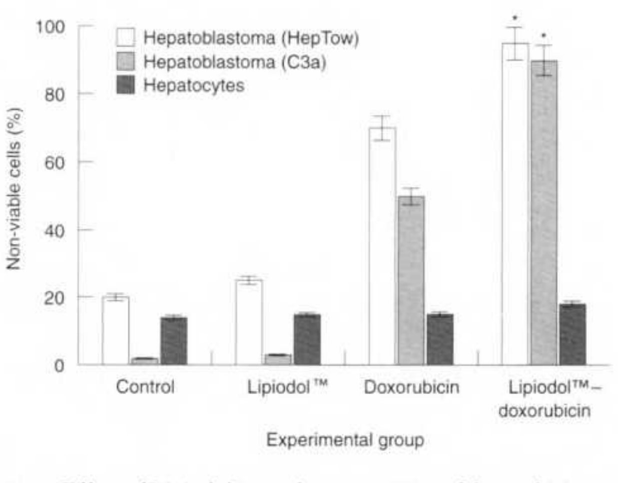

Fig. 4 Effect of Lipiodol™ on the cytotoxicity of doxorubicin to liver cell lines. Values are mean(s.d.). $^*P < 0{\cdot}05$ *versus* same cell line treated with doxorubicin (analysis of variance)

Discussion

Doxorubicin is an effective anticancer anthracycline commonly used in the treatment of solid tumours[17]. Previous investigations have evaluated the use of intra-arterial epirubicin–Lipiodol™ in the treatment of hepatocellular carcinoma[18] and the disposition and pharmacokinetics of epirubicin when administered with Lipiodol™[18,19]. Tissue levels of doxorubicin are significantly increased within the area of the tumour, in comparison to non-tumorous areas of the same liver, when the drug is administered with Lipiodol™[20–23]. A few centres have used this form of treatment in children with hepatoblastoma, with variable results[8–11]. However, there has been no previous objective assessment of its mechanism of action, and little objective rationale for its efficacy.

The amino ring of doxorubicin, which lies perpendicular to the planar anthracycline ring, also lies perpendicular to the DNA ring, allowing the molecule to intercalate DNA, by binding its amino group to the sugar-phosphate backbone of the DNA[24]. There is considerable debate about the other likely primary cytotoxic mechanism of action of these drugs, such as interference with topoisomerase II or the formation of free radicals. The anthracyclines can undergo both one- and two-electron reduction via nicotinamide adenine dinucleotide phosphate reductases to yield the corresponding semiquinone or dihydroquinone respectively. These in turn can reduce molecular oxygen to superoxide and/or hydrogen peroxide, which can yield hydroxyl radicals causing direct cell damage.

Lipiodol™ provides an improved doxorubicin delivery vehicle that allows selective targeting of the drug to the tumour by peripheral arterial embolization[25–27], and improves intracellular delivery by acting as a reservoir that allows prolonged action. The data presented in this study show that uptake of doxorubicin by hepatoblastoma cell lines (C3a, HepTow) in culture occurred mainly into the nucleus and increased over 48 h. There was enhanced uptake of doxorubicin by the same cell lines when doxorubicin was used in combination with Lipiodol™. Uptake of Lipiodol™ by liver cells is by a process of pinocytosis as membrane-bound vesicles. The enhanced uptake correlated with enhancement of cytotoxicity of doxorubicin on hepatoblastoma cells in culture by the addition of Lipiodol™.

This study has confirmed an enhanced uptake of doxorubicin by the addition of Lipiodol™ to hepatoblastoma cells in culture, and supports the potential use of Lipiodol™ chemoembolization in children with advanced or inoperable hepatoblastoma. Taking into consideration the *in vitro* limitations of these experiments, Lipiodol™–doxorubicin targeted treatment may have therapeutic implications for advanced hepatoblastoma by enhancing the intracellular uptake and cytotoxicity of doxorubicin *in vivo*. This may enable a reduction in the total dose administered and reduce side-effects. Clinically safe preoperative Lipiodol™ chemotherapy has enabled significant tumour shrinkage and subsequent resection of 'irresectable' or advanced hepatoblastoma[10,11]. In addition, there was no marked chemotherapeutic agent-induced toxicity noted during the observation period. The outcome of the proposed international studies using transarterial chemoembolization with Lipiodol™[28] with various cytotoxic agents will certainly shed further light on the value of this mode of therapy in children with irresectable hepatoblastoma and other cancers[29].

Acknowledgement

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Surgical repair of ruptured thoracic and thoracoabdominal aortic aneurysms

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Background: Rupture is the single most common cause of death in patients with thoracic aortic and thoracoabdominal aneurysm (TAA/TAAA) and is almost uniformly fatal.
Methods: This was a retrospective review of patients admitted to a single practice with rupture of a TAA/TAAA between 1993 and 2000.
Results: Twenty-two consecutive patients with a leaking TAA/TAAA were identified. The aetiology of rupture was either secondary to a degenerative TAAA or a type B dissection. Seventeen patients underwent surgery; one had a Crawford extent I, seven an extent II, one an extent III and two an extent IV TAAA. Six patients had an acute type B dissection with rupture in the upper descending thoracic aorta. The 30-day survival rate was 88 per cent (15 of 17 patients). Actuarial survival at 1 year in patients who had surgery was 65 per cent. Survival at 1 year for all presenting patients who consented to surgery was 40 per cent. Median survival was greater than 36 months.
Conclusion: As a result of improving medical care, more patients with a contained rupture of a TAA/TAAA may present for treatment. Surgery is complex and requires specialist teams for optimal care.

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Introduction

The lack of an applicable screening investigation for thoracic aneurysms, together with the absence of symptoms before rupture, means that many patients first present when the aneurysm leaks[1,2]. Rupture is the single most common cause of death in patients with thoracic aortic and thoracoabdominal aneurysm (TAA/TAAA)[3], and is almost uniformly fatal[4]. In a small number of patients rupture may be contained by pleura or peritoneum, allowing survival for several hours[5]. Providing that the diagnosis can be made rapidly, there is an opportunity for an attempt at surgical repair.

Although emergency surgery is a recognized treatment for ruptured infrarenal abdominal aortic aneurysm, there are few reports of surgical management for ruptured TAA/TAAA[6–8]. The surgery is technically challenging and difficult to perform as an emergency, when time-consuming thoracolaparotomy, visceral mobilization and perfusion techniques to afford spinal cord protection need to be instituted simultaneously with effective early control of the leaking aneurysm. Results in this group of patients vary widely, with published mortality rates ranging from 15 to 40 per cent in dedicated cardiovascular centres[6–8]. In the UK, the separation of cardiothoracic and vascular surgical specialties may limit access for these patients.

As untreated rupture is fatal, survival is dependent upon surgery. If satisfactory survival can be achieved despite the difficulties, treatment of ruptured TAA/TAAA becomes justifiable.

The present study records an experience of a single centre in the management of patients with ruptured TAA/TAAA.

Patients and methods

This was a retrospective review of patients admitted to a single practice with rupture of a TAA/TAAA between 1993 and 2000. Information was retrieved from case notes and from a prospectively maintained computerized database. Follow-up was performed by telephone communication with the patient's general practitioner.

Results

Twenty-two consecutive patients with a leaking TAA/TAAA were identified (13 men; mean age 70 (range 47–

83) years). The diagnosis was made in all patients by contrast-enhanced computed tomography. All patients had obvious periaortic haematoma surrounding the aneurysm or dissection, and had free blood within the pleura or peritoneum at operation. Seventeen patients underwent surgery.

Transfer details

All patients were transferred from other hospitals between 5 and 36 h following presentation. The mean transfer distance was 38 (range 22–129) miles. All patients had undergone initial fluid resuscitation and imaging in their local hospitals. Following stabilization, patients were transferred rapidly; fluid resuscitation was recommenced if the patient became shocked.

Preoperative status

Common presenting features were chest pain (ten patients), back pain (six) or both (six). Four patients had a systolic blood pressure of less than 90 mmHg on arrival, despite fluid resuscitation. Mean urine output was 19 (range 0–80) ml/h. Three patients had a reduced level of consciousness. One was paraplegic before operation, and one had electrocardiographic changes compatible with acute myocardial ischaemia.

The mean haematocrit was 0·33 (range 0·27–0·42). The mean preoperative serum urea concentration was 8·1 (range 3·1–20·4) µg/l and that of creatinine was 116 (range 69–273) µg/l.

Preoperative mortality

One of the 22 patients, who had a degenerative TAAA, declined operation and died 9 days later. Twenty-one patients were counselled and consented for emergency surgery. Four patients with a leaking degenerative aneurysm died from free rupture in the interval between evaluation and anaesthesia. Patients were scheduled for emergency surgery unless they were pain free and haemodynamically stable with a contained leak, in which case they were scheduled for operation the next morning. None of the latter patients died before surgery. Seventeen patients (12 men; mean age 69 (range 47–78) years) underwent surgery.

Findings at surgery

Of the 17 patients who had surgery, one had a Crawford extent I, seven an extent II, one an extent III and two an extent IV TAAA (*Fig. 1*). Six patients had an acute type B dissection with rupture in the upper descending thoracic aorta. In all patients rupture was predominantly contained in the mediastinum, extrapleural space or the retroperitoneum; all had free extraluminal blood.

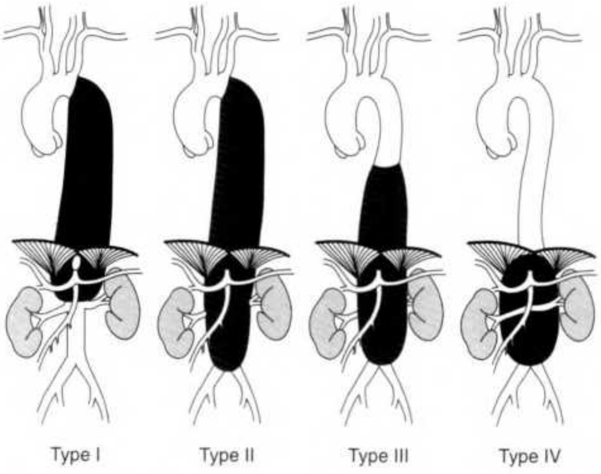

Fig. 1 Crawford classification of thoracic and thoracoabdominal aneurysms[9]

Table 1 Surgical techniques

Incision	
Median sternotomy and thoracotomy	6
Trans-sternal (clamshell)	2
Thoracolaparotomy	9
Bypass technique	
None	3
Left heart	4
Full	9
Partial left femoral artery/left femoral vein	1
Hypothermic circulatory arrest	9
Timing (min)*	
Hypothermic circulatory arrest	23 (3–49)
Cardiopulmonary bypass	117 (18–253)
Cross-clamp time	35 (20–69)

*Values are mean (range)

Anaesthetic and operative technique

Surgical techniques and operative timings are summarized in *Table 1*. All patients received dexamethasone and mannitol before circulatory arrest or aortic cross-clamping. Four patients early in the series received thiopentone. At the time of the study patients did not undergo cerebrospinal fluid drainage, although this is now routine practice. Routine renal protective therapy included mannitol 1 mg/kg in the cardiopulmonary bypass circuit, dopamine 3 mg per kg per min and frusemide 5 mg/h infusions, and postoperative monitoring of cardiac output. TAAA repair

Table 2 Morbidity after thoracic aortic and thoracoabdominal aneurysm repair

	No. of patients
Tracheostomy	5
Ileus	1
Ischaemic bowel	1
Haemofiltration	2
Transient paraparesis	1
Transient confusion	1
Permanent spinal cord injury	1

was performed using the endoaneurysmorrhaphy technique of Crawford *et al.*[9]. The aorta was replaced using a polyester–gelatin Gelweare® graft (Sulzer Vascutek®, Inchinnan, UK) graft with separate reimplantation of intercostals, coeliac axis, superior mesenteric and renal arteries, according to aneurysm anatomy. Red cell salvage techniques were used routinely whenever possible. Mean transfused volume was 3000 (range 752–4610) ml. In patients undergoing full thoracoabdominal repair, visceral perfusion was checked thoroughly at the end of the operation. The mean duration of surgery was 451 (range 305–620) min. The surgery required a mean of 12 (range 4–25) units packed red cells, 5 (range 0–25) units fresh frozen plasma and 3 (range 0–12) units of platelets.

Bypass techniques

In three patients no perfusion technique could be used owing to the urgent need to control haemorrhage. In these patients repair took place during a period of proximal aortic clamping and distal exsanguination, salvaging and reinfusing of shed blood. In other patients distal perfusion techniques were selected according to individual procedures. In all the type B dissection operations and in three of the TAAA repairs it was felt inadvisable to clamp the aortic arch, so full cardiopulmonary bypass was employed and an open proximal anastomosis was constructed during hypothermic circulatory arrest. Arterial return was then transferred to the graft, the graft was clamped and proximal body perfusion was recommenced. The clamp position was then adjusted following each subsequent anastomosis allowing sequential reperfusion of intercostal arteries, visceral arteries and the lower body circulation.

In the five operations in which proximal clamping was possible, either left heart bypass or partial cardiopulmonary bypass was used. When a clamp could not be applied at the distal extent of the aneurysm, the duration of bypass was limited to the period of proximal anastomosis, after which the remaining reconstruction was performed using a proximal clamp and distal exsanguination with red cell salvage[10,11].

Outcome

Mortality

One patient with a type III TAAA, who arrested after anaesthetic induction and required external cardiac massage until bypass was established, could not be weaned from cardiopulmonary bypass. One patient with a type B dissection had palpable coronary artery disease at operation and required considerable inotropic support to be weaned from bypass. This patient died on the first day after operation. All the other patients survived to hospital discharge (88 per cent). There was a considerable mortality rate during the year after repair from other cardiovascular or respiratory causes; the actuarial survival at 1 year in patients who had surgery was approximately 53 per cent (nine of 17). Survival at 1 year for all patients who consented to surgery was around 40 per cent (nine of 22).

Follow-up ranged between 2 and 70 months; one patient was lost to follow-up. Kaplan–Meier analysis of the operative group showed a median survival of greater than 36 months.

Morbidity

All major postoperative morbidity is detailed in *Table 2*.

After operation patients spent a mean of 13 (range 1–52) days in intensive care. One patient presented with a paraparesis that persisted after operation. One further patient had a postoperative paraparesis that recovered to allow limited ambulation.

Two patients required reoperation. One had surgical intervention for bleeding and survived. A second underwent laparotomy and stoma formation after colectomy for ischaemic colitis and survived.

The mean maximum postoperative creatinine level was 206 (range 69–471) µg/l. Two patients required temporary haemofiltration, but none needed permanent renal support.

Discussion

Up to 50 per cent of patients with a contained rupture of a TAA/TAAA survive for 6–24 h following the initial event allowing time for surgical repair[5].

In the present review, patients with or without haemodynamic compromise who reached the operating theatre had an early and mid-term survival that justified the major resource consumption consequent on attempted salvage[12]. Survival rates were comparable to those achieved for ruptured abdominal aortic aneurysm surgery[13].

Thoracic aortic rupture is generally into the free pleural cavity leading to rapid exsanguination and death[14]. Occasionally rupture occurs towards the mediastinum or is contained by the parietal pleura[6–8].

Recent improvements in the elective operative management of TAA/TAAA have lead to an increase in both 1- and 5-year survival rates (over 70 and 50–60 per cent respectively)[15]. Only a few studies have examined survival following emergency repair of TAA/TAAA. The mortality rate was higher than that after elective surgery (less than 10 per cent for elective[16] compared with 10–40 per cent for emergency repair[6–8]).

Recently, Mastroroberto *et al.*[7] followed 47 consecutive patients with a TAA/TAAA over a 5-year interval. Nineteen required emergency surgery, 12 had a rupture and seven an acute dissection. The 30-day mortality rate was 42 per cent, with two late deaths. The median survival was 36 months for patients who left hospital alive.

In a series of 23 operations for TAAA rupture, Bradbury *et al.*[6] reported good in-hospital survival in patients who were not haemodynamically compromised on admission. As in the current series, a high rate of postoperative morbidity was noted. Bradbury *et al.* concluded that patients with rupture of a type II TAAA associated with haemodynamic compromise had such a poor prognosis that surgical intervention should not be offered.

In contrast, von Segesser *et al.*[8] reported survival in 100 consecutive patients with TAAA, 33 with rupture. They did not find any statistically significant difference between the 30-day mortality rate after elective (6 per cent) or emergency (15 per cent) operation. Similarly, Velazquez *et al.*[17] reported a similar series of 110 TAAA repairs, including 33 emergency operations, with no significant difference in outcome between elective and emergency presentations (overall mortality rate 13 per cent).

Surgical outcome would therefore appear to vary for patients with a ruptured TAAA. This is likely to reflect diverse influences such as time from rupture to referral, severity of haemodynamic compromise and complexity of surgery. Some of these factors are difficult to examine in the literature. It would appear, however, that it is possible to save some patients with a ruptured TAA/TAAA. These patients require considerable resources to be available, including surgical/anaesthetic expertise and a range of perfusion techniques including full and partial cardiopulmonary bypass.

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Original article

Accelerated postoperative recovery programme after colonic resection improves physical performance, pulmonary function and body composition

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Background: Postoperative organ dysfunction contributes to morbidity, hospital stay and convalescence. Multimodal rehabilitation with epidural analgesia, early oral feeding, mobilization and laxative use after colonic resection has reduced ileus and hospital stay.

Methods: Fourteen patients receiving conventional care (group 1) and 14 patients who had multimodal rehabilitation (group 2) were studied before and 8 days after colonic resection. Outcome measures included postoperative mobilization, body composition by whole-body dual X-ray absorptiometry, cardiovascular response to treadmill exercise, pulmonary function and nocturnal oxygen saturation.

Results: Defaecation occurred earlier (median day 1 *versus* day 4) and hospital stay was shorter (median 2 *versus* 12 days) in patients who had multimodal treatment. Lean body and fat mass decreased in group 1 but not in group 2. Exercise performance decreased by 44 per cent in group 1 but was unchanged in group 2. A postoperative increase in heart rate (HR) response to exercise was avoided in group 2. Pulmonary function decreased in group 1 but not in group 2. There was less nocturnal postoperative hypoxaemia in group 2. Cardiac demand–supply (HR/oxygen saturation ratio) increased in group 1 but not in group 2.

Conclusion: Multimodal rehabilitation prevents reduction in lean body mass, pulmonary function, oxygenation and cardiovascular response to exercise after colonic surgery.

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Introduction

Colonic and other major surgical procedures are associated with postoperative pain, paralytic ileus, reduced pulmonary function and loss of muscle mass and function[1], all of which may contribute to postoperative morbidity and need for hospital stay. It was shown previously in a descriptive study that a multimodal rehabilitation programme, including continuous epidural analgesia, early oral nutrition, enforced mobilization, and cisapride and laxative use, reduced ileus and postoperative hospital stay to 2–3 days after colonic resection[2].

The aim of the present study was to assess the changes in postoperative organ function in patients undergoing colonic resection with multimodal rehabilitation and to compare the results with those of patients receiving conventional care.

Patients and methods

The study was prospective, controlled and non-randomized. Fourteen consecutive patients from the Department of Surgical Gastroenterology, Copenhagen University Hospital, Gentofte received conventional care (group 1) and 14 consecutive patients from the Department of Gastroenterology, Hvidovre University Hospital, Hvidovre received multimodal rehabilitation (group 2) after elective open right hemicolectomy or sigmoid colon resection. Exclusion criteria were age less than 18 years, patients with pacemaker or other implanted metal, patients requiring a stoma or an anastomosis less than 12 cm from

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The Editors have satisfied themselves that all authors have contributed significantly to this publication

Table 1 Protocol for anaesthesia, surgery and rehabilitation programme after colonic resection with conventional care (group 1) and multimodal rehabilitation (group 2)

	Conventional care (group 1)	Multimodal rehabilitation (group 2)
Anaesthesia	Premedication: oral diazepam 10 mg Epidural catheter T8–T10 Carbocaine 2% 4 + 4 ml with adrenaline Carbocaine 2% 4 ml with adrenaline hourly General anaesthesia Fentanyl 0·1 mg Thiomebumal 3–5 mg/kg Rocuronium Oxygen–nitrous oxide–sevoflurane Dextran 70 (Macrodex®) 500 ml Saline 3000 ml (maximum)	No premedication Epidural catheter Right hemicolectomy T6–T7 Sigmoid resection T9–T10 Test: lignocaine 2% 3 ml with adrenaline Bupivacaine 0·5% 6 + 6 ml Bupivacaine 0·25% 5 ml 2 hourly at operation Morphine 2 mg if < 70 years old Morphine 1 mg if ≥ 70 years old General anaesthesia Remifentanil 1 μg per kg per min Propofol 2–4 mg per kg per h Cisatracium 0·15 mg/kg Hydroxyethyl starch (HAES®) 500 ml Saline 1500 ml (maximum) Ondansetron 4 mg Ketorolac 30 mg Bupivacaine 0·25% 20 ml (incision)
Surgery	Median laparotomy	Transverse or curved incision[2]
After operation	Continuous epidural analgesia (3 days) Bupivacaine 0·25% 4 ml/h Morphine 0·2 mg/h Breakthrough pain Intramuscular or intravenous morphine After removal of epidural catheter Morphine 10 mg orally on request No standard care programme; fluid, food, mobilization and discharge depending on the attending surgeon Postoperative nasogastric tube depending on surgeon who performed the operation	Continuous epidural analgesia (2 days) Bupivacaine 0·25% 4 ml/h Morphine 0·2 mg/h Breakthrough pain Ibuprofen 600 mg orally Bupivacaine 0·12% 6 ml epidurally Morphine 10 mg orally (last choice) Food, protein drink approximately 60–80 g protein per day and mobilization from the day of surgery following a well defined nursing care programme[2] Day of surgery start Acetaminophen (slow release) 2 g 12 hourly Magnesia 1 g 12 hourly Cisapride 20 mg 12 hourly First day after operation Remove bladder catheter in the morning Second day after operation Remove epidural catheter in the morning Discharge after lunch

the anus, and patients unable to perform the preoperative test programme. The local ethics committee approved the study and informed patient consent was obtained before investigation according to the Helsinki II declaration.

The perioperative care programme is detailed in *Table 1*. Mobilization (hours out of bed per day) was assessed daily by the patient during the first week after operation by means of a questionnaire.

Pulmonary function (forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and peak expiratory flow (PEF)) was measured with a vitalograph (Micro Plus Spirometer MS03; Micro Medical, Rochester, UK) before operation and 6 h, 24 h, 48 h and 8 days after surgery with the patient in the sitting position.

Body composition (lean body mass (LBM), fat mass (FM) and weight) was measured before and 8 days after surgery by whole-body dual X-ray absorptiometry (DXA)[3,4] (XR 36 DXA scanner™; Nordland, Fort Atkinson, Illinois, USA) with the patient in a supine position wearing light clothing without shoes, 2 h after a light breakfast and voiding. The scanner was calibrated before scanning. All scans were performed in Hvidovre University Hospital by L.B. and H.W.H. DXA parameters were obtained from measurements on femur. Body-weight was also measured on hospital scales (Liebra; N. C. Nielsen, Copenhagen, Denmark).

The cardiovascular response to treadmill exercise was assessed until exhaustion or the heart rate (HR) reached 120

Table 2 Demographics of patients undergoing colonic resection with conventional care (group 1) or multimodal rehabilitation (group 2)

	Conventional care (group 1; $n = 14$)	Multimodal rehabilitation (Group 2; $n = 14$)
Age (years)	64 (52–79)	74 (33–94)
Weight (kg)	70 (55–137)	72 (42–105)
Height (cm)	171 (157–185)	166 (143–175)
ASA		
I	4	1
II	7	6
III	3	7
Type of surgery		
Right hemicolectomy	5	10
Sigmoid resection	9	4
Preoperative haemoglobin (mmol/l)	7·8 (5·7–9·1)	7·5 (5·0–9·4)
Blood loss (ml)	225 (100–2000)	200 (0–1000)
0–24 h intravenous fluid (ml)	3750 (3000–5500)	3325 (2150–4000)*

Values are median (range). ASA, American Society of Anesthesiologists. $^*P < 0\cdot05$ *versus* conventional care (Mann–Whitney U test)

per min, before operation and 8 days after surgery. The tests were performed on an electronic treadmill (J 502; Tunturi®, Piispanristi, Finland). The start speed was adjusted according to body-weight; a 1° increase in elevation corresponded to a 5-W workload increase. The patient walked for 3 min at each workload to reach steady state. After each 3-min period the HR was measured and the treadmill was elevated. The workload and energy performed were calculated as described previously[5]. All tests were performed in Hvidovre University Hospital by L.B. and D.H.J.

Oxygen saturation (constant hypoxaemia: mean saturation ($Sp\mathrm{O}_2$), duration of $Sp\mathrm{O}_2$ below 90 per cent; episodic hypoxaemia: number of episodes in which the oxygen saturation dropped 5 per cent or more for at least 10 s within 2 min) and HR were measured continuously during one night before surgery and during the first two nights after surgery (23.00 hours to 07.00 hours) by pulse oximetry (Nellcor N-3000 L™ Nellcor Puritan Bennett, Pleasanton, California, USA). Oxygen saturation data were downloaded to a computer (Score Software version 1.0C 1997; Nellcor).

Mental function was assessed before operation and 24 h, 48 h and 8 days after surgery by the Hodkinson[6] modification of the original Roth–Hopkins test[7], which consisted of 26 questions that tested short- and long-term memory, recognition, orientation and cognitive function.

Pain at rest and during movement from the supine to the sitting position was scored every 4 h (except at night) for the first 2 days after operation, daily in the morning from postoperative day 2 to 7 and weekly for a total of 4 weeks using a scale from 0 to 3 (0, no pain; 1, slight pain; 2, moderate pain; 3, severe pain). Nausea and fatigue were scored using a similar scale and at the same intervals during the first and fourth weeks after operation. The area under the curve (AUC) for each variable was calculated and used for statistical evaluation.

Serum albumin and plasma C-reactive protein (CRP) were analysed before operation and on day 8 after surgery.

Data are presented as median (range). Comparisons were done using the Mann–Whitney and Wilcoxon signed rank tests. Friedman two-way analysis of variance was used to compare differences for repeated data within groups. $P \leqslant 0\cdot05$ was considered statistically significant.

Results

Demographic data are shown in *Table 2*. There were no significant differences between groups, except for a smaller volume of perioperative intravenous fluids in group 2. Postoperative defaecation occurred on day 4 (2–7) in group 1 and on day 1 (0–2) in group 2 ($P < 0\cdot001$). Postoperative hospital stay was 12 (5–21) days in group 1 and 2 (2–4) days in group 2 ($P = 0\cdot001$).

Mobilization

The total time out of bed during the first postoperative week was 87 (64–121) h in group 2 and 61 (19–84) h in group 1 ($P < 0\cdot01$) (*Fig. 1*).

Body composition

Perioperative changes in total body-weight within each group and between the groups were insignificant. LBM on the femur decreased significantly in group 1 by 429 g (7 per cent) ($P < 0\cdot05$), but increased insignificantly by 158 g (2

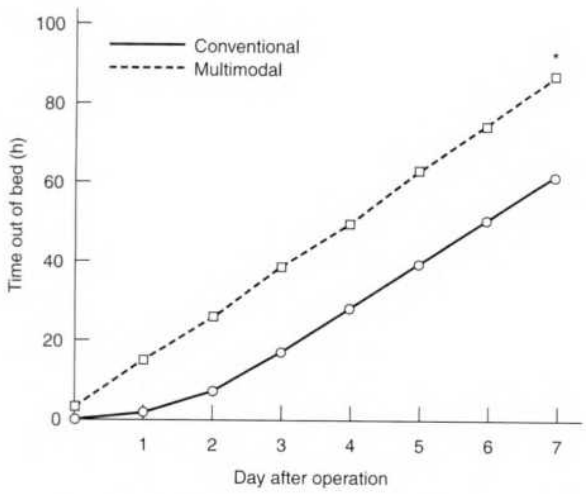

Fig. 1 Mobilization during the first week after elective colonic resection in patients who had conventional care (group 1) and multimodal rehabilitation (group 2). $^*P < 0\cdot05$ *versus* conventional care (Mann–Whitney test)

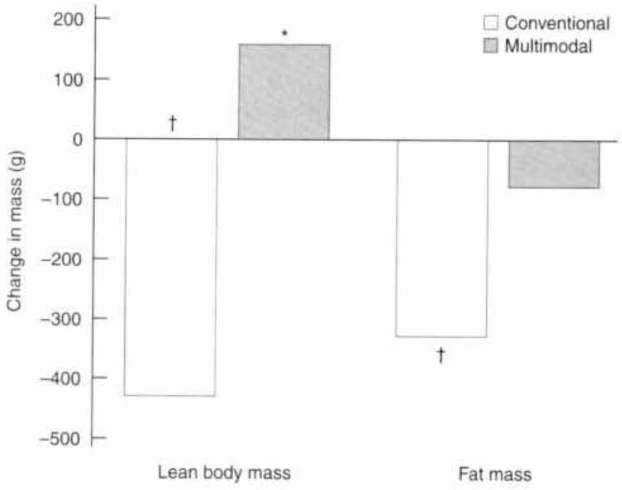

Fig. 2 Change in femoral lean body mass and fat mass from before operation to 1 week after colonic resection in patients who had conventional care (group 1) and multimodal rehabilitation (group 2). $^*P < 0\cdot05$ *versus* conventional care (Mann–Whitney test), $^\dagger P < 0\cdot05$ from before operation to 8 days after surgery in conventional care group (Wilcoxon)

per cent) in group 2 (*Fig. 2*) ($P < 0\cdot05$ between groups) (Mann–Whitney test). FM on the femur decreased significantly in group 1 by 329 g (6 per cent) ($P < 0\cdot05$), but insignificantly by 77 g (1 per cent) in group 2 (*Fig. 2*) ($P > 0\cdot05$ between groups) (Mann–Whitney test).

Treadmill exercise

Before operation two patients in group 1 and five patients in group 2 were exhausted before reaching a HR of 120 per min, compared with eight patients in group 1 and six patients in group 2 after operation. *Fig. 3* shows the amount of work performed in the two groups before and after operation until exhaustion or with the HR at 120 per min. The amount of work performed decreased significantly by 44 per cent in group 1 ($P < 0\cdot05$) and insignificantly by 12 per cent in group 2 ($P < 0\cdot05$ between groups). The work performed per increase in HR decreased significantly by 0·33 W per heartbeat (27 per cent) in group 1 during the first postoperative week ($P < 0\cdot05$), but insignificantly by 0·08 W per heartbeat (8 per cent) in group 2.

Oxygen saturation

Median $S\text{pO}_2$ decreased on the second postoperative night in group 1 ($P < 0\cdot05$), but not in group 2 (*Table 3*). The time spent with an $S\text{pO}_2$ below 90 per cent was higher on the second postoperative night than before operation in group 1 ($P < 0\cdot05$), but no change occurred in group 2. The number of hypoxaemic episodes in the two groups was no different ($P > 0\cdot05$), although there were more episodes of hypoxaemia on the second night after operation in group 2 (*Table 3*). HR changes within and between groups were not significant (*Table 3*). The postoperative change in HR/$S\text{pO}_2$ ratio, as an indicator of the cardiac demand (HR)–supply (oxygen) balance is shown in *Fig. 4*. The HR/$S\text{pO}_2$ ratio increased significantly in group 1 ($P < 0\cdot05$), but was unchanged in group 2.

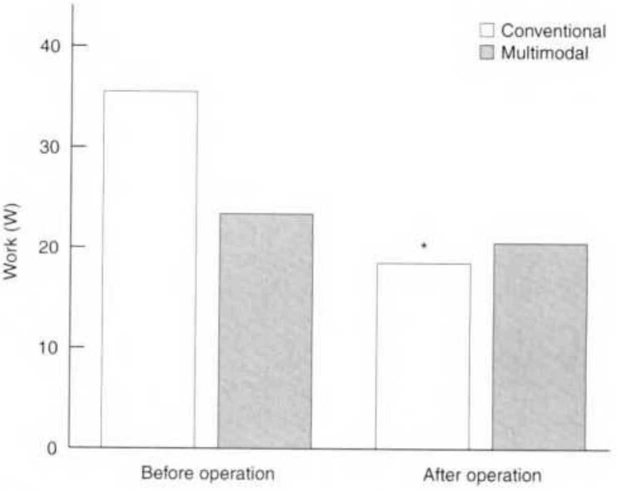

Fig. 3 Amount of work performed until exhaustion or heart rate reached 120 per min before and 1 week after colonic resection in patients who had conventional care (group 1) and multimodal rehabilitation (group 2). The decrease in amount of work performed was significantly different between groups ($P < 0\cdot05$). $^*P < 0\cdot05$ *versus* before operation in conventional care group (Mann–Whitney test)

Table 3 Median oxygen saturation, constant hypoxaemia, episodic hypoxaemia and heart rate before operation and during the first two nights after surgery (23.00 to 07.00 hours) in patients undergoing colonic resection with conventional care (group 1) or multimodal rehabilitation (group 2)

	Conventional care (group 1; n = 14)	Multimodal rehabilitation (Group 2; n = 14)
Median Spo_2 (%)		
Before operation	96 (94–99)	95 (89–97)
1st postop. night	95 (92–98)	95 (90–98)
2nd postop. night	93 (86–97)*	94 (88–98)
$Spo_2 \leqslant 90\%$ (min)		
Before operation	0 (0–12)	0 (0–257)
1st postop. night	0 (0–44)	0 (0–260)
2nd postop. night	58 (0–402)*	0 (0–322)
Desaturation (events $\geqslant$ 10 s)		
Before operation	2 (0–139)	4 (0–175)
1st postop. night	3 (0–380)	0 (0–138)
2nd postop. night	21 (0–274)	3 (0–102)
Heart rate (per min)		
Before operation	69 (57–95)	76 (51–102)
1st postop. night	75 (54–101)	76 (59–98)
2nd postop. night	77 (56–109)	74 (58–102)

Values are median (range). Spo_2, oxygen saturation; postop., after operation. $^*P < 0{\cdot}05$ *versus* before operation in conventional group (Wilcoxon test). There were no differences between groups before operation

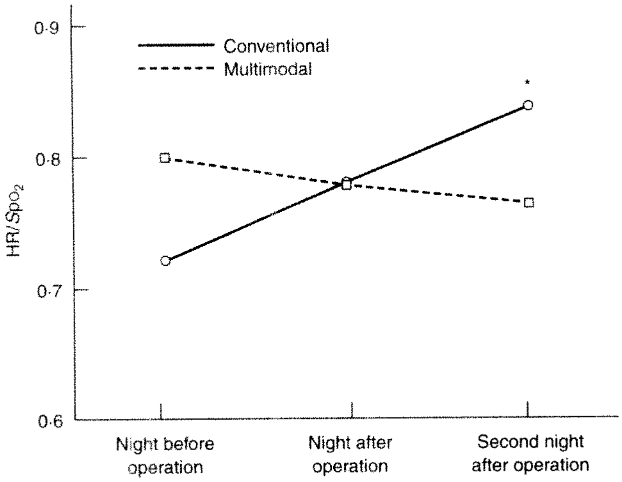

Fig. 4 Change in heart rate (HR)/oxygen saturation (Spo_2) ratio in the early postoperative period, measured during one night before surgery and during the first two nights after operation (23.00 hours to 07.00 hours) in patients who had conventional care (group 1) and multimodal rehabilitation (group 2). $^*P < 0{\cdot}05$ *versus* before operation in conventional care group (Mann–Whitney test)

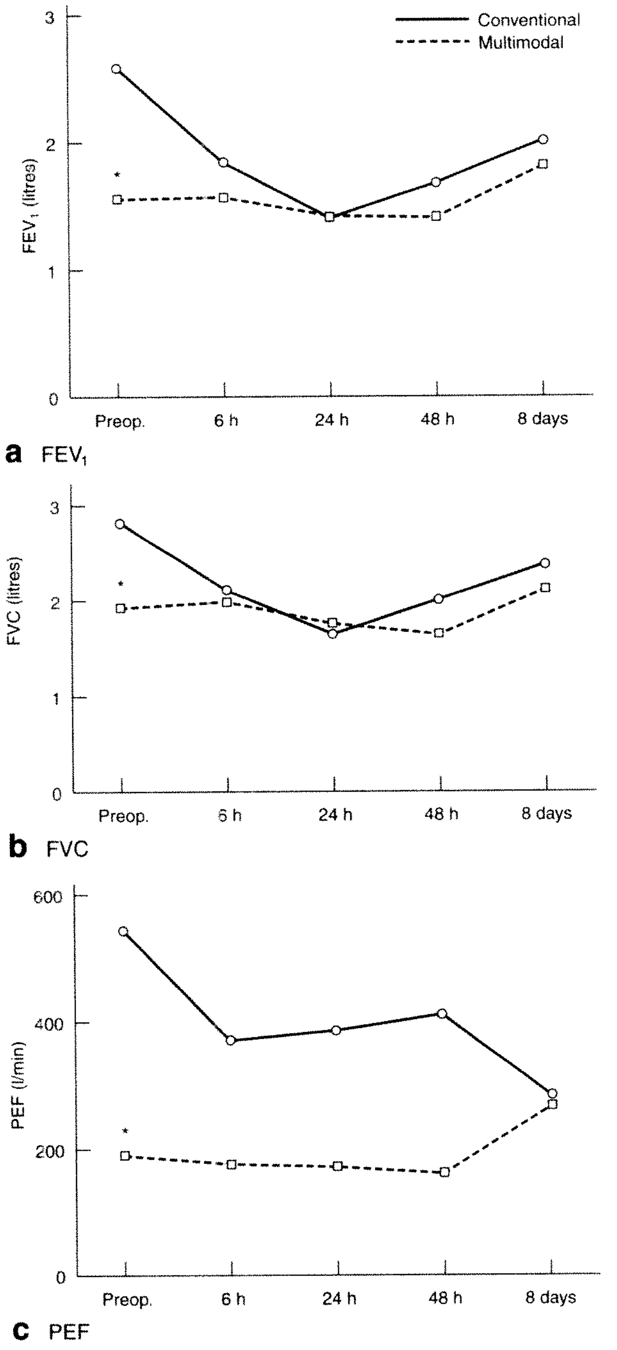

Fig. 5 Changes in pulmonary function during the early period after colonic resection in patients who had conventional care (group 1) and multimodal rehabilitation (group 2). **a** Forced expiratory volume in 1 s (FEV_1), **b** forced vital capacity (FVC) and **c** peak expiratory flow (PEF). FEV_1, FVC and PEF were impaired during the perioperative period in group 1 ($P < 0{\cdot}05$). $^*P < 0{\cdot}05$ between groups before operation

Pulmonary function

Before operation patients in group 1 had significantly better pulmonary function (FEV_1, FVC and PEF) than those in group 2 ($P < 0.05$). Patients in group 1 experienced impairment in pulmonary function during the first week after operation ($P < 0.05$). In contrast, there was no change in pulmonary function during the first postoperative week in group 2 (*Fig. 5*).

Mental test

There were no perioperative differences within or between groups in mental test scores.

Pain, fatigue and nausea

Group 1 had significantly more pain (AUC 30) at rest during the first 2 days after operation than group 2 (AUC 10) ($P < 0.05$), but no differences in pain between the groups were observed during mobilization, in fatigue during the first 30 days or in nausea during the first postoperative week.

Serum albumin and plasma C-reactive protein

Median serum albumin level decreased significantly from 572 to 513 μmol/l in group 1 ($P < 0.01$), but insignificantly from 538 to 502 μmol/l in group 2. Median plasma CRP concentration increased from below 95 to 122 nmol/l in group 1 and from 103 to 203 nmol/l in group 2 during the first postoperative week (*P* not significant).

Morbidity and readmissions

In group 1 one patient had a postoperative wound infection and dehiscence, one patient had postoperative ileus and required treatment with a nasogastric tube for 4 days, and one patient was readmitted for nausea and social reasons on day 22. In group 2 one patient was readmitted on day 14 with mechanical bowel obstruction, one patient was readmitted for 1 day on day 13 because of a urinary tract infection, and one patient was treated in the outpatient clinic for a wound infection.

Discussion

The results of this prospective non-randomized study showed that the usual postoperative organ dysfunction (ileus, pulmonary dysfunction, catabolism and decreased work performance) did not occur after colonic resection with multimodal rehabilitation compared with conventional postoperative care. These results have important clinical implications because postoperative organ dysfunction contributes to morbidity and length of hospital stay[1].

It may be argued that the study should have been randomized, but it was impossible to randomize and blind patients and nurses to multimodal rehabilitation or conventional care in the same ward. When the necessary cultural changes involved in a multimodal rehabilitation programme[1] have been introduced it is difficult, if not unethical, to randomize patients to traditional care with no specific attention towards early mobilization and oral nutrition, since these care principles have been proven to be valid[1]. Furthermore, revised care practices, including avoidance of gastrointestinal tubes, drains and prolonged urinary catheterization, are impossible to randomize in a ward where care has already been adjusted to a fast-track programme[1].

The improved early active mobilization with more hours out of bed during the first postoperative week in patients with multimodal rehabilitation may have contributed to several positive outcomes including improved pulmonary function and oxygen saturation[8], and less reduction of postoperative LBM and work performance[9]. The institution of early enforced postoperative mobilization requires an optimized pain relief programme, in which continuous epidural analgesia with a mixture of local anaesthetic and low-dose opioid is most effective[10]. Another important factor is patient education, and the introduction of the well defined nurse care programme in which daily requirements for mobilization are followed[2]. Interestingly, both study groups received continuous epidural postoperative analgesia, but pain was less in the group that had active rehabilitation during the first 2 days. The explanation for this may be the reduced duration of postoperative ileus associated with less discomfort and pain, facilitated by epidural analgesia, early nutrition and laxative use.

The demonstrated improvement in pulmonary function may have important clinical implications in reducing pulmonary morbidity, as shown in an earlier study of 100 consecutive patients (including high-risk patients) undergoing colonic resection without pulmonary morbidity[2,11]. Although epidural analgesia *per se* may improve pulmonary function and outcome[12], the combination of continuous epidural analgesia with enforced early mobilization may represent a further means of improving pulmonary outcome. The improved oxygen saturation brought about by early mobilization[8] may secondarily have important clinical implications by reducing postoperative cardiac morbidity, cerebral dysfunction and wound complications[13]. Multimodal rehabilitation may have important effects on cardiac morbidity since the HR/SpO_2 ratio is reduced, reflecting a more favourable cardiac energy supply–demand balance. Further data are required to document such potential advantages, but previous experience of 100 consecutive patients with a median age of 73 years has demonstrated a very low (less than 3 per cent) wound and cardiac morbidity rate[2,11].

The observed reduction in postoperative loss of LBM and work performance may be a consequence of several factors associated with multimodal rehabilitation. Even a short period of immobilization will lead to muscle atrophy, negative nitrogen balance and loss of LBM[9]. Also, early oral nutrition with protein drinks may have facilitated preservation of LBM. The preservation of LBM and work performance may have important implications for elderly patients undergoing major surgery, since such patients already have a decreased physiological reserve capacity[14] which may increase the risk of postoperative morbidity. The femur was used to assess changes in LBM and FM by DXA since fluid retention after abdominal surgery occurs mainly in the trunk[15]. In contrast, a large part of the muscle mass is localized on the femur and thus may represent the 'true' LBM compared with 'total' LBM in the postoperative state.

The physiological response to exercise decreased after operation in patients undergoing conventional rehabilitation as demonstrated previously[16]. This change did not occur in patients undergoing multimodal rehabilitation, even though these patients were older and less fit before operation. However, the patients who had multimodal rehabilitation had been home for a median of 6 (range 4–6) days compared with the continued hospitalization in the conventional care group, and the documented increased mobilization may therefore have preserved physical performance.

Another feature of the multimodal rehabilitation programme is the reduction in paralytic ileus from 3–5 days to 1–2 days[2]. The pathogenesis of postoperative ileus is multifactorial[10], but continuous epidural analgesia with local anaesthesia has been shown to reduce ileus[10,17]. Early oral feeding, mobilization and use of laxatives may also have contributed, although the relative role of these factors has not been established from randomized controlled trials[17]. The reduction of ileus may facilitate early oral feeding, which otherwise has been shown to improve physical performance and LBM[18,19], while even short-term starvation decreases work capacity[20].

The present small and non-randomized study provides substantial evidence in support of the hypothesis that aggressive postoperative rehabilitation is superior to conventional postoperative care. The findings should serve as a stimulus to further investigation of the concept of multimodal postoperative rehabilitation and to the initiation of large multicentre comparative studies.

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Dual publication

Readers may care to review the following two articles: 'Blankensteijn JD, Lindenburg FP, van der Graaf Y, Eikelboom BC. Influence of study design on reported mortality and morbidity rates after abdominal aortic aneurysm repair. *Br J Surg* 1998; **85:** 1624–30' and 'Blankensteijn JD. Mortality and morbidity rates after conventional abdominal aortic aneurysm repair. *Semin Interv Cardiol* 2000; **5:** 7–13'.

The Editors find a remarkable similarity in the text and tables of these articles; data shown in the later paper are the same as those shown in Figure 1 of the *BJS* paper. While the *BJS* article is referenced in the bibliography of the later paper, there is no acknowledgement of the previous 1998 publication. Our publishers, Blackwell Publishing Limited, have no record of any communication with either Dr Blankensteijn or the publishers of *Seminars in Interventional Cardiology*, Harcourt Publishers Limited.

The Editors wish to make clear the responsibilities of those intent on dual publication. They must take heed of copyright regulations. They should also offer the simple courtesy of acknowledging the prior publication of work in another journal; merely citing an article in the bibliography of the later paper does not constitute authority or permission to re-publish.

The Editors

Original article

Fate of the rectum in patients undergoing total colectomy for Crohn's disease

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Background: This study aimed to analyse disease recurrence and fate of the rectum in patients who had a total colectomy for Crohn's disease.

Methods: One hundred and forty-four patients who had a total colectomy for Crohn's colitis were reviewed retrospectively. Ileorectal anastomosis (IRA) was performed in 118 patients, while 26 never had an IRA after colectomy because of severe anorectal lesions. Factors associated with recurrence and rectal preservation failure were studied.

Results: The probability of clinical recurrence after IRA was 58 and 83 per cent at 5 and 10 years respectively. The probability of rectal preservation at 5 and 10 years was 70 and 63 per cent after colectomy, and 86 and 86 per cent after IRA, respectively. Patients with extraintestinal manifestation had a higher risk of recurrence and of rectal preservation failure. Previous ileal involvement was associated with a higher rate of ileal recurrence after IRA. After IRA, prophylactic treatment with 5-aminosalicylic acid was associated with a lower rate of recurrence and of failure to preserve the rectum.

Conclusion: Overall, 63 per cent of patients had a functioning IRA 10 years after total colectomy. Absence of extraintestinal manifestation and prophylactic treatment with 5-aminosalicylates after IRA were the main factors associated with long-term rectal preservation.

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Introduction

In patients with extensive Crohn's colitis refractory to medical therapy, the operation usually performed is a total colectomy. A majority of patients will have an ileorectal anastomosis (IRA) at the same time or secondarily. Recent reports have stated that approximately 75 per cent of them will maintain a functional anastomosis at 10 years[1–3]. However, a number of patients will never have an IRA after colectomy because of the severity of rectal and/or perianal Crohn's disease. Frequently, these patients are not taken into account to analyse the risk of rectal preservation failure after total colectomy, since most studies only consider patients in whom an IRA has been performed.

To evaluate the functional outcome of patients who need a total colectomy for Crohn's disease, a retrospective study of recurrence of the disease after IRA, and of rectal preservation failure after total colectomy and after IRA, was performed. Predictive criteria of postoperative long-term outcome were analysed. These criteria could be useful for the allocation of early postoperative therapeutic strategies, including immunosuppressive drugs, to improve the rate of rectal preservation after total colectomy.

Patients and methods

Population studied

Between 1980 and 1997, 144 patients had a total colectomy for Crohn's disease. Characteristics of patients are shown in *Table 1*. Ninety-four patients were operated on because of resistance to intensive treatment including steroids, 45

The Editors have satisfied themselves that all authors have contributed significantly to this publication

Table 1 Characteristics of the 144 patients at the time of colectomy

Sex ratio (F : M)	78 : 66
Age (years)*	31 (16–86)
Duration of disease (years)*	2 (0–21)
Location of disease†	
Pure colonic	115 (80)
Ileocolonic	29 (20)
Perianal lesions	23 (16)
Presence of granuloma†	55 (38)
Presence of extraintestinal manifestations†‡	40 (28)
Skin	14
Mouth	9
Eye	2
Joint	28

*Values are median (range); †values in parentheses are percentages. ‡Eleven patients had two manifestations and one patient had three manifestations

Table 2 Severity of ileal, rectal and perineal lesions at the time of colectomy and ileorectal anastomosis

	At colectomy ($n = 144$)	At ileorectal anatomosis ($n = 118$)
Rectal involvement		
None	23 (16)	64 (54)
Erythema	25 (17)	32 (27)
Superficial ulcerations	44 (31)	12 (10)
Deep ulcerations	44 (31)	0 (0)
Unknown	8 (6)	10 (8)
Ileal involvement		
None	114 (79)	110 (93)
Ulceration	21 (15)	3 (3)
Stenosis	8 (6)	2 (2)
Unknown	1 (1)	3 (3)
Perianal lesions		
None	116 (81)	108 (92)
Mild	18 (12)	5 (4)
Severe	5 (3)	0 (0)
Unknown	5 (4)	5 (4)

Values in parentheses are percentages

because of chronic active colitis and five because of a complication (abscess, one; occlusion, two; peritonitis, two). *Table 2* summarizes the state of the rectum, ileum and perineum before surgery.

At the time of colectomy, 61 per cent of the patients had rectal ulceration. Ileal stenosis was found in eight patients (6 per cent), while 21 (15 per cent) had ileal ulceration. Among the 23 patients with perianal disease, five had severe lesions, including rectovaginal fistula (three) and deep anal ulceration with incontinence (two). Between colectomy and IRA, two patients with rectovaginal fistula had a successful surgical repair allowing a subsequent IRA, while two patients with mild perianal lesions at colectomy developed severe perianal involvement with sphincter destruction and became unsuitable for a secondary IRA. After colectomy, all patients with rectal lesions received daily mesalazine and/or steroid enemas. At the time of IRA, only 10 and 4 per cent of the patients still had rectal ulceration or active perianal lesions respectively. After IRA, 5-aminosalicylic acid and azathioprine were given to prevent disease recurrence in 34 patients (29 per cent) and 27 patients (23 per cent) respectively.

Surgical procedures

Among the 144 patients who had a total colectomy, 26 (18 per cent) never had an IRA after colectomy because of either severe intractable rectal lesions (21 patients), severe perianal lesions (three) or a combination of both (two). They all had a secondary proctectomy at a median of 15 (range 2–36) months after colectomy (*Fig. 1*). Twelve of them had a permanent ileostomy, while an ileal pouch–anal anastomosis was performed in the other 14 patients. Ileal pouch–anal anastomosis was considered in some patients without a present or past history of ileal or perianal involvement[4].

One hundred and eighteen patients (82 per cent) had an IRA at the time of colectomy (17 patients) or secondarily (101), a median of 3 (range 2–12) months after colectomy. Postoperative anastomotic leakage occurred in six patients (5 per cent). No secondary proctectomy was related to postoperative complications. In 13 patients, proctectomy had to be performed because of intractable proctitis (ten patients), severe perianal disease (two) or a combination of both (one) a median of 4 (range 0·1–16) years after IRA. Nine of these patients had a permanent ileostomy and four had an ileal pouch–anal anastomosis. Among the 105 patients who maintained a functional anastomosis by the end of the follow-up, six had an iterative IRA for ileal recurrence. Also, two rectovaginal fistula repairs and a sphincteroplasty for incontinence were performed successfully.

Follow-up

After surgery, patients were reviewed at 6-month intervals for the first year, and at yearly intervals thereafter. Endoscopic examination was performed when clinical symptoms suggestive of disease recurrence were present.

Data analysis

Outcome events were clinical recurrence and failure of rectal preservation. Clinical recurrence was defined as the

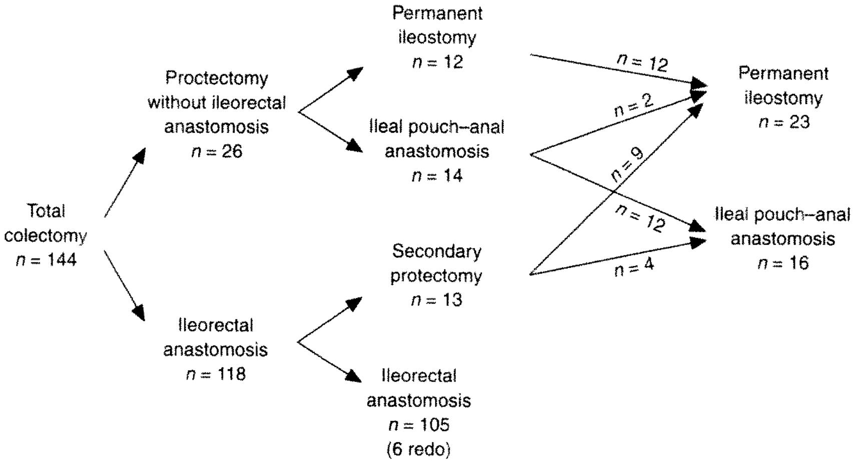
Total colectomy $n = 144$
Proctectomy without ileorectal anastomosis $n = 26$
Ileorectal anastomosis $n = 118$
Permanent ileostomy $n = 12$
Ileal pouch–anal anastomosis $n = 14$
Secondary protectomy $n = 13$
Ileorectal anastomosis $n = 105$ (6 redo)
$n = 12$
$n = 2$
$n = 9$
$n = 12$
$n = 4$
Permanent ileostomy $n = 23$
Ileal pouch–anal anastomosis $n = 16$

Fig. 1 Outcome of the 144 patients after total colectomy

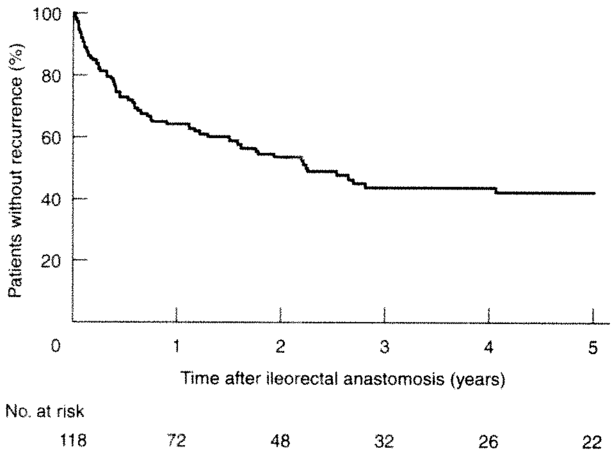

Fig. 2 Probability of the absence of clinical recurrence after ileorectal anastomosis (n = 118) (Kaplan–Meier analysis)

reappearance of symptoms confirmed by endoscopic features of Crohn's disease. Failure of rectal preservation was defined as the need for a proctectomy after colectomy or after IRA.

Probabilities of clinical recurrence and of rectal preservation were calculated using the Kaplan–Meier method. Probabilities of rectal and ileal recurrence were also analysed. The time to clinical recurrence was calculated from the date of IRA. The time to rectal preservation failure was calculated from the date of colectomy for all the patients and from the date of IRA in patients who had an IRA, to the date of proctectomy or of the lastest follow-up. The influence of concomitant variables on time to clinical recurrence and rectal preservation failure was examined using the Cox proportional hazards model according to the following variables: sex, age and duration of disease at the time of colectomy, disease location and severity of lesions at the time of colectomy or IRA, presence of granuloma and extraintestinal manifestation, and prophylactic treatment after colectomy (aminosalicylates, immunosuppressive agents). The proportional hazards model was first applied to study the influence of each factor on time to clinical recurrence or rectal preservation failure. A multivariate analysis was then applied using a stepwise procedure to those variables with $P < 0{\cdot}10$ in the univariate analysis, using BMDP statistical software (BMDP, Los Angeles, California, USA). In the multivariate procedure, $P < 0{\cdot}05$ was considered as the level of significance. Quantitative variables are expressed as median (range). Relative risks (RRs) are presented as mean estimate with a 95 per cent confidence interval (c.i.).

Results

Median duration of follow-up after total colectomy until proctectomy or the last news was 5 (range 0·6–17·0) years. Median duration of follow-up after IRA until proctectomy or the last news was 3·8 (range 0·1–16·4) years.

Clinical recurrence after ileorectal anastomosis

Clinical recurrence was diagnosed in 72 of the 118 patients who had an IRA. Endoscopy at the time of recurrence showed lesions located at the rectum in 49 patients (68 per cent), at the ileum in three (4 per cent) and at both sites in 20 (28 per cent). The probability of clinical recurrence was 58 and 83 per cent at 5 and 10 years respectively (*Fig. 2*). In

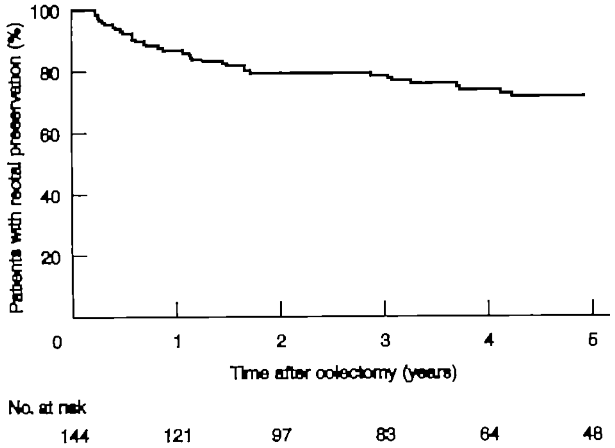

Fig. 3 Probability of rectal preservation after total colectomy (n = 144) (Kaplan–Meier analysis)

both univariate and multivariate analysis, the presence of extraintestinal manifestation was associated with a higher risk of clinical recurrence after IRA (RR 2·1 (95 per cent c.i. 1·2 to 3·7); P = 0·01). In contrast, use of prophylactic 5-aminosalicylates after IRA was associated with a lower risk of recurrence (RR 0·5 (95 per cent c.i. 0·3 to 0·9); P = 0·03).

The probability of rectal and ileal recurrence at 5 and 10 years after IRA was 53 and 73 per cent, and 17 and 22 per cent, respectively. In univariate analysis, the probability of rectal recurrence was higher in patients without previous ileal involvement (P = 0·02) and in patients who did not receive prophylactic 5-aminosalicylic acid (P = 0·03); in multivariate analysis, use of prophylactic 5-aminosalicylates was the only factor associated with a lower risk of rectal recurrence (RR 0·5 (95 per cent c.i. 0·3 to 0·9); P = 0·02). The probability of ileal recurrence was higher in the presence of granulomas (P = 0·02) and in patients with ileal involvement at the time of colectomy (P < 0·001); in multivariate analysis, previous ileal involvement remained the only factor associated with a higher risk of ileal recurrence (RR 4·4 (95 per cent c.i. 1·7 to 11·6); P = 0·004).

Failure of rectal preservation

Among the 144 patients, 39 had a proctectomy. The probability of rectal preservation after colectomy was 70 and 63 per cent at 5 and 10 years respectively (*Fig. 3*). In the 118 patients who had an IRA, the probability of rectal preservation was 86 per cent at both 5 and 10 years. In univariate analysis, the presence of extraintestinal manifestation was strongly associated with a higher rate of rectal preservation failure both after colectomy (P = 0·008) and after IRA (P = 0·004). The presence of perianal lesions at the time of colectomy, but not at the time of IRA, was also associated with a worse outcome (P = 0·009). Absence of prophylactic 5-aminosalicylates after IRA was associated with a higher risk of rectal preservation failure (P = 0·01). In multivariate analysis, the presence of extraintestinal manifestation was the only variable associated with a higher risk of rectal preservation failure, both after colectomy (RR 2·4 (95 per cent c.i. 1·2 to 4·5); P = 0·01) and after IRA (RR 3·1 (95 per cent c.i. 1·1 to 8·7); P = 0·04).

Functional outcome

At the end of the follow-up, the median number of bowel movements was 3·5 (range 1–12) per day in the 105 patients with a functioning IRA. Twenty-one patients were receiving azathioprine and 19 patients 5-aminosalicylates to prevent disease recurrence.

Discussion

After total colectomy in patients with extensive Crohn's colitis, IRA is usually the preferred option even if it is associated with a higher risk of disease recurrence and reoperation than proctocolectomy with permanent ileostomy[5–8]. Ileal pouch–anal anastomosis has been proposed as an alternative with good results reported in some studies[4]. However, this operation can be attempted only in a selected subgroup of patients with neither anal nor ileal involvement.

Postoperative recurrence in Crohn's disease has been studied extensively, mainly in patients with ileal and right colonic involvement after partial ileocolonic resection. In such patients, recurrence is always located at the anastomosis and/or at the neoterminal ileum. The role of the faecal stream in its pathogenesis has been highlighted by Rutgeerts *et al.*[9]. Conversely, recurrence in patients with extensive colonic involvement after total colectomy and IRA has been studied less extensively. The present results show that such recurrence was mostly located at a rectal site. Ileal recurrence was observed with a higher frequency in patients with ileitis before surgery, and was usually associated with rectal recurrence. These results suggest that the location of the disease tends to remain constant over time in a given patient.

This outcome after IRA is consistent with recent published series, showing a sensitive improvement in IRA success rates over the past 10 years (*Table 3*). Surprisingly, this improvement parallels an increased rate of clinical recurrence. One explanation might be a better management of recurrence over the years. The wider use of 5-aminosalicylic acid and azathioprine after IRA might have minimized the intensity of recurrence. In contrast to

Table 3 Outcome of functioning ileorectal anastomosis: review of the literature

			Rate of clinical recurrence (%)		Rate of functioning IRA (%)	
Reference	Year	No. of patients	5 years	10 years	5 years	10 years
Buchmann *et al.*[10]	1981	105	–	–	–	70†
Ambrose *et al.*[11]	1984	63	–	64	–	71‡
Ritchie[8]	1990	59	34	49	–	–
Longo *et al.*[12]	1992	118	–	63	86	48
Chevallier *et al.*[13]	1993	83	47*	57*	77*	63*
Pastore *et al.*[1]	1997	42	42§	–	74*	65*
Yamamoto *et al.*[3]	2000	65	–	–	86*	78*
Bernell *et al.*[2]	2001	106	47*	58*	–	76¶
Present series		144	58*	83*	86*	86*

*Kaplan–Meier analysis. †At 7·6 years; ‡at 9·5 years; §at 6·5 years; ¶at 12·5 years. IRA, ileorectal anastomosis

previous studies, the cumulative rate of functioning IRA remained constant after 5 years in this study, suggesting that recurrence occurring late during follow-up is at present well controlled by medical treatment.

The present series provides further information regarding the outcome of patients after total colectomy for Crohn's disease. Most studies include patients at the time of IRA and therefore do not consider patients who had a total colectomy with initial rectal preservation but in whom an IRA will never be performed. In this study, 18 per cent of the patients had such an outcome mainly because of the severity of rectal involvement and to a lesser extent because of severe perianal lesions.

Factors associated with a higher risk of rectal preservation failure have been studied extensively, with controversial results. As in other studies[12–14], no relationship was found between the severity of rectal lesions before colectomy and the risk of rectal preservation failure. This is a justification for refraining from one-stage proctocolectomy in patients with rectal lesions, unless the distensibility of the rectum is obviously compromised[10,15]. Perianal involvement has no predictive value for outcome if treated before IRA[16]. Newly available therapies aimed at perianal healing, such as monoclonal antibody to tumour necrosis factor α[17] or surgical repair using fibrin tissue adhesive or sealant[18], could be of benefit in that particular setting.

In contrast with previous results[12,19], patients with previous ileal involvement did not have a higher risk of rectal preservation failure. In the present series, these patients were at higher risk of ileal recurrence, often associated with rectal recurrence. Pure ileal recurrence can be treated by an iterative resection and a new IRA[11], and therefore is not likely to compromise rectal preservation. The only factor strongly associated with a higher risk of rectal preservation failure was the presence of extraintestinal manifestation. This factor has not been reported in previous studies. Extraintestinal manifestations are more common in patients with Crohn's colitis than in patients with disease confined to the small bowel[20]. As these manifestations were also associated with a higher risk of clinical recurrence, their presence may reflect more active inflammatory disease.

Postoperative prevention of recurrence with 5-aminosalicylates remains controversial. A recent meta-analysis has found a significant but limited benefit of these agents on clinical recurrence[21]. Most of the patients in the placebo-controlled randomized trials had ileocolonic resection, and the effect of 5-aminosalicylic acid on clinical recurrence after IRA cannot be deduced from these studies. The present results suggest that prophylactic 5-aminosalicylic acid can reduce the rate of rectal recurrence and of rectal preservation failure after IRA. The effect of prophylactic azathioprine on recurrence after IRA was not statistically significant perhaps because of the small number of patients receiving this treatment. Because of the functional consequences of recurrence and the risk of proctectomy, prophylactic immunosuppressants should be especially considered in patients with IRA. Controlled trials comparing 5-aminosalicylic acid and azathioprine/6-mercaptopurine are needed.

In conclusion, at 10 years after total colectomy for Crohn's colitis or ileocolitis, 37 per cent of the patients had a secondary proctectomy, either because it was not possible to perform an IRA or because of disease recurrence after IRA. After IRA, and despite a high rate of clinical recurrence (83 per cent at 10 years), rectal preservation was achieved in 86 per cent of the patients at 10 years. Prophylactic treatment including 5-aminosalicylic acid and immunosuppressive agents could improve the long-term outcome of these patients.

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Original article

Treatment of advanced gastric cancer by palliative gastrectomy, cytoreductive therapy and postoperative intraperitoneal chemotherapy

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Background: The treatment options for the 10–20 per cent of patients with gastric cancer who present with peritoneal dissemination are extremely limited and no standard approach exists.

Methods: The feasibility of using intraperitoneal chemotherapy to treat gastric cancer with intra-abdominal gross residual lesions after palliative gastrectomy with maximal cytoreduction was investigated. Early postoperative intraperitoneal chemotherapy started on the day of operation with 5-fluorouracil 500 mg/m^2 and cisplatin 40 mg/m^2 (days 1–3) over a 4-week interval.

Results: Of the 53 patients enrolled between July 1994 and December 1998, 49 were eligible. The progression-free survival (PFS) was 7 months and the overall survival was 12 months. In multivariate analysis, performance status was the only significant defining factor for PFS ($P = 0{\cdot}009$). The predominant toxicity was neutropenia and nausea/vomiting. The relative dose intensity of 5-fluorouracil and cisplatin was 89 and 63 per cent respectively.

Conclusion: Performance status emerged as a major determining factor for prognosis and patient selection for early postoperative intraperitoneal chemotherapy in patients with advanced gastric cancer after maximally cytoreductive surgery.

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Introduction

Gastric carcinoma is the main cause of cancer-related death in Korea[1]. The treatment options for those with peritoneal dissemination are extremely limited and no standard approach exists. In one study the median survival for peritoneal carcinomatosis of gastric cancer treated by surgery alone was only 1 month[2]. There have been several reports advocating the benefit of aggressive surgery even for far advanced gastric cancers[3–5].

Randomized trials have rationalized combination chemotherapy for irresectable gastric cancer[6,7]. However, a large number of patients presented with resistant or metastatic peritoneal disease after systemic chemotherapy[8]. The major reasons for chemotherapy failure were lack of achievement of a cytotoxic drug concentration as well as a limited chemosensitivity of gastric cancer. Since the first documentation of the pharmacodynamics of intraperitoneal chemotherapy[9], the proposed pharmacokinetic advantages and acceptable toxicity profile have now been demonstrated[10–13]. A peak peritoneal concentration higher than the plasma level was achieved by intraperitoneal administration. The area under the curve values for intraperitoneal and intravenous infusions were equivalent, and accelerated the intraperitoneal chemotherapy with acceptable toxicity[10–13].

The management of peritoneal seeding by gastrectomy plus perioperative intraperitoneal chemotherapy has been shown to provide a survival advantage[14]. Unfortunately, the small number of subjects in this study, the absence of a well randomized control group, an unstandardized surgical procedure and the technological requirements of intraperitoneal chemotherapy have clouded the potential value of this treatment[15]. Few studies have been designed to determine whether chemotherapy following palliative resection could improve a patient's recovery[16,17]. This study investigated the value of using intraperitoneal chemotherapy in patients with gross residual lesions after maximal cytoreduction.

Patients and methods

Patient selection

Patients were enrolled in the study between July 1994 and December 1998. The eligibility criteria were: (1) histologically proven gastric adenocarcinoma; (2) no haematogenous metastatic lesions; (3) Eastern Clinical Oncology Group scale performance status 2 or less; (4) aged 65 years or younger; (5) no previous abdominal operation; (6) adequate bone marrow, liver, cardiac and renal function; (7) no other severe medical conditions or active malignancies; and (8) no previous systemic chemotherapy. All patients had tumour beyond the designed resection area or intra-abdominal seeding at the time of abdominal exploration. Numerous distant peritoneal metastases, fixed lymph nodes with a positive frozen biopsy in nodes around the middle colic artery and para-aortic nodes, or involvement of the rectal shelf were considered to represent distant irresectable sites and resulted in exclusion from the study.

Pathological staging

Pathological classification was done according to the criteria of the American Joint Committee on Cancer (1998). The peritoneal (P) stage was adopted from the Japanese General Rules for Gastric Cancer Study[15]: no peritoneal seeding (P_0), metastasis to the adjacent peritoneum (P_1), a few metastases to distant peritoneum (P_2) and numerous metastases to distant peritoneum (P_3).

Palliative resection

The palliative resection consisted of gastrectomy, extended lymphadenectomy (D_2 resection) and cytoreductive surgery including resection of an adjacent organ, peritonectomy or metastatectomy. In order to standardize the procedure, all procedures were performed by one surgical team. Any operation that leaves residual microscopic (R_1) or macroscopic (R_2) tumour behind the resection margin, tumour bed or lymphatic drainage area is considered to be palliative according to the Union Internacional Contra la Cancrum classification[18]. All of the patients in this study had gross residual tumour in the abdominal cavity (R_2) in spite of maximal cytoreduction. Subsequent early postoperative intraperitoneal chemotherapy was started on the day of operation.

Early postoperative intraperitoneal chemotherapy

The technique described by Cunliffe and Sugarbaker[19] was used. Immediately after operation, the catheter was flushed with 1000 ml isotonic saline every hour for the first 4 h and then every 4 h until intraperitoneal chemotherapy began.

After flushing, 500 ml saline was placed into the cavity. 5-Fluorouracil (5-FU) 500 mg/m^2 and cisplatin 40 mg/m^2 each mixed in 500 ml isotonic saline were administered through the catheter for 30 min. The catheter was clamped until the next day's dose was due, when the remaining fluid was drained. The same treatment was repeated for three consecutive days, giving a total dose of 1500 mg/m^2 5-FU and 120 mg/m^2 cisplatin in each cycle. If there was no evidence of disease progression, chemotherapy was repeated every 4 weeks for at least six cycles to a maximum of 12 cycles.

Follow-up evaluation during chemotherapy

The dose was reduced by 25 per cent if the haematological and/or non-haematological toxicity was more than grade 3 in the previous cycle. If toxicity exceeding grade 3 persisted at the time of the next cycle, chemotherapy was delayed on a weekly basis for up to 4 weeks until recovery. If the patient refused further intraperitoneal chemotherapy or unacceptable toxicity occurred, including intractable catheter-site infection, the intraperitoneal procedure was stopped. Conventional systemic chemotherapy or observation occurred after removing the intraperitoneal catheter. Computed tomography (CT) of the abdominopelvis performed every three cycles was used to detect disease progression.

Follow-up evaluation after chemotherapy

During the follow-up period, any suspected recurrence was confirmed by biopsy whenever possible. Typical nodules identified by liver ultrasonography, CT or chest radiography, or lytic areas on the radioisotope bone scan, were accepted as recurrence without histological confirmation when a definite change was shown with respect to baseline studies.

Endpoint and statistical analysis

The follow-up period was defined as the time from the day of operation to December 1999. The progression-free survival was the interval from the first day of intraperitoneal chemotherapy to the time of progression.

The pretreatment characteristics and efficacy were analysed with χ^2 and t tests. Survival curves were estimated

Table 1 Patient characteristics

	No. of patients
Patients entered	53
Eligible patients	49
Median (range) age (years)	41 (22–65)
Sex ratio (M : F)	28 : 21
Performance status (ECOG scale)	
0	6
1	31
2	12
Operation type	
Subtotal	11
Total	38
Histology	
Adenocarcinoma	
Well differentiated	2
Moderately differentiated	2
Poorly differentiated	26
Signet ring cell carcinoma	14
Undifferentiated carcinoma	1
Mucinous carcinoma	4
Lauren classification	
Intestinal	6
Diffuse	34
Mixed	9
Gross (Borrman) type	
I	1
II	6
III	22
IV	20
Residual lesion	
Tumour bed	10
Distant site	22
Both	17
P stage	
P_0	10
P_1	19
P_2	13
P_3	7

ECOG, Eastern Cooperative Oncology Group

Table 2 Overview of the patients' treatment course

	No. of patients
Treatment completed without progression	10
6 cycles	7
12 cycles	3
Progression during treatment	28
Within 6 cycles	22
Over 6 cycles	6
Treatment interruption without disease progression	11
Patient refusal	3
Toxicity or complication	6
Observation	2
Switch to systemic chemotherapy	4
Treatment-related death	2

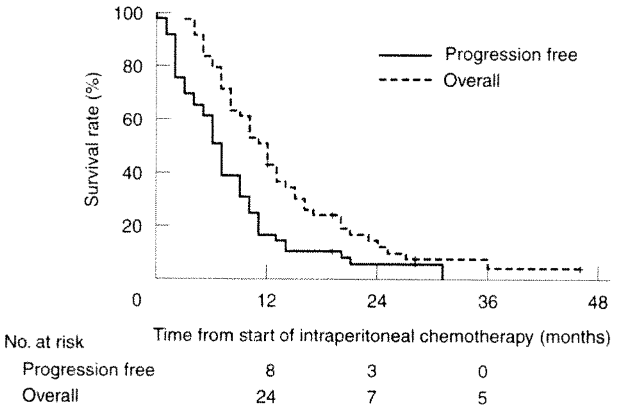


Fig. 1 Progression-free and overall survival curves for all 49 patients. Median progression-free and overall survival were 7 and 12 months respectively

using the Kaplan–Meier technique and the Cox proportional hazard regression model.

Results

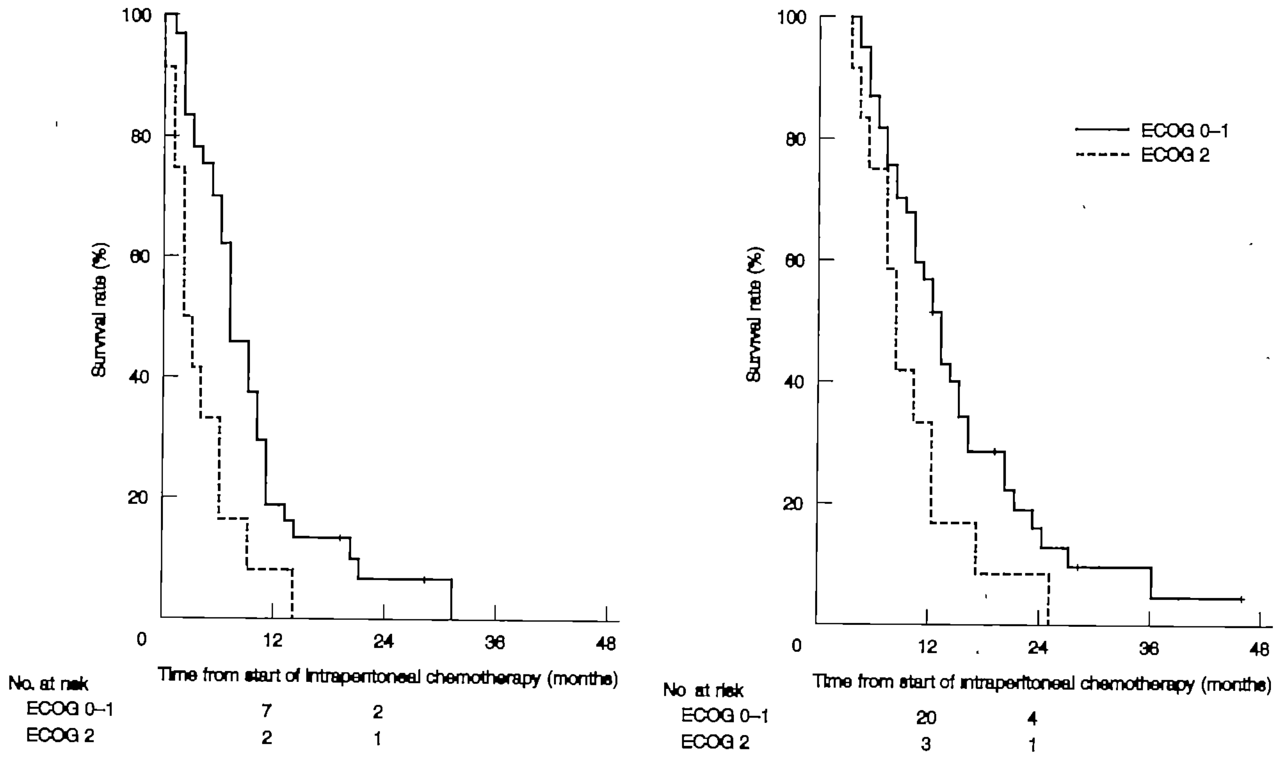
Patient characteristics

Of the 53 patients who received palliative resection during the enrolment period, 49 were eligible. Three patients refused intraperitoneal chemotherapy and one was aged over 65 years. A total of 239 treatment courses was administered (median 5 (range 1–12) courses per patient). There were 28 men and 21 women with a median age of 41 (range 23–65) years. Thirty-seven patients had a performance status of 0–1. Thirty-four patients had the diffuse type of gastric cancer according to Lauren's classification. A residual lesion was present in the tumour bed in ten patients, at a distant site in 22 patients and at both sites in 17 patients. With respect to the P stage, 20 patients were P_{2-3}.

A subtotal gastrectomy was performed in 11 patients and a total gastrectomy in 38 patients. Twenty patients received additional organ resection, including the spleen or colon. The mean volume of the main tumour in the stomach measured bidimensionally was 74 (range 6–306) ml. The mean number of removed and tumour-involved lymph nodes was 43 (range 13–81) and 21 (range 11–64) respectively. The clinical characteristics and treatment course are summarized in *Tables 1* and *2* respectively.

Dose intensity

Eighty-eight (46 per cent) of 190 subsequent courses were delayed because of adverse reactions. The median course



a Progression-free survival

b Overall survival

Fig. 2 a Progression-free and b overall survival curves according to performance status. Median (95 per cent confidence interval) progression-free survival was 7 (5–9) and 2 (0–4) months for Eastern Clinical Oncology Group (ECOG) 0–1 and ECOG 2 respectively ($P = 0.005$, log rank test). Respective values for overall survival were 13 (11–15) and 8 (8–10) months ($P = 0.06$, log rank test)

interval was 4 (range 4–8) weeks. The median actual administered dose intensity of 5-FU was 333 (range 181–375) mg per m^2 per week and that of cisplatin was 19 (range 11–29) mg per m^2 per week, which corresponded to 89 (range 48–100) and 63 (range 37–97) per cent of the planned dose for each drug.

Progression and survival

At a median follow-up of 37 (range 12–65) months, progressive disease was confirmed in 43 of the 49 patients. Three patients had a locoregional pattern of progression, 25 had intra-abdominal progression (carcinomatosis), five had haematogenous metastasis and ten had a mixed pattern. Progression was not affected by gender, P stage, age, Lauren type or Borrman type. The performance status showed a marginal relation to progression ($P = 0.08$).

Twenty-eight patients had disease progression during intraperitoneal chemotherapy, with a median of 4 (range 2–10) cycles until progression. Ten patients completed six cycles of chemotherapy without evidence of progression, of whom three received up to 12 cycles (*Table 2*).

The median progression-free survival was 7 (95 per cent confidence interval 6 to 8) months and the median overall survival was 12 (95 per cent confidence interval 10 to 14) months (*Fig. 1*). Univariate analysis revealed a significant relationship between performance status and progression-free survival ($P = 0.005$). A marginal relationship was noted between performance status, gross type and overall survival ($P = 0.06$) (*Fig. 2*). The site of residual disease did not affect survival. In the multivariate analysis, only performance status was a significant defining factor for progression-free survival ($P = 0.009$) (*Table 3*).

Toxicity

The predominant haematological toxicity was neutropenia, and the most common non-haematological toxicity was nausea and vomiting (*Table 4*). Nausea, vomiting and renal impairment were transitory and recovered with conservative care.

Table 3 Univariate and multivariate analyses of clinical factors and survival

	Progression-free survival		Overall survival	
	Univariate	Multivariate	Univariate	Multivariate
Gender (male *versus* female)	0·19		0·07	
Age (≤ 50 *versus* > 50 years)	0·33		0·12	
Operation type (with *versus* without organ resection)	0·63		0·81	
Borrman type (I–III *versus* IV)	0·13		0·06	
Performance status (ECOG scale) (0–1 *versus* 2)	0·005	0·009	0·06	0·09
Lauren type (intestinal *versus* diffuse)	0·96		0·78	
P stage (0–1 *versus* 2–3)	0·92		0·54	
Lymph nodes involved (adjacent *versus* distant)	0·78		0·46	
Initial residual lesion (tumour bed *versus* distant)	0·43		0·24	
Dose intensity (5-FU) (above *versus* below median)	0·21		0·47	
Dose intensity (cisplatin) (above *versus* below median)	0·40		0·52	

ECOG, Eastern Clinical Oncology Group; 5-FU, 5-fluorouracil

There were two treatment-related deaths. One was due to febrile neutropenia with septic shock and the other was related to refractory salt-losing nephropathy. Nine patients had interrupted chemotherapy, three of whom refused further treatment of their own accord; in the remainder the interruption resulted from catheter-related complications. All of these patients had the catheter removed and four were switched to systemic chemotherapy. The median number of treatment cycles in these nine patients was 2 (range 1–5).

Table 4 Haematological and non-haematological toxicity

	No. of patients				
Toxic effect*	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Haematological					
Leucopenia	18	8	16	6	1
Neutropenia	18	4	10	10	7
Anaemia	8	0	33	6	2
Thrombocytopenia	39	0	3	6	1
Non-haematological					
Nausea/vomiting	11	11	17	10	0
Diarrhoea	38	6	4	1	0
Neuropathy	43	2	4	0	0
Hepatic	28	10	9	2	0
Renal	38	5	5	1	0
Infection	40	2	3	3	1
Constipation	39	0	7	3	0
Abdominal pain	28	10	7	4	0

Discussion

Systemic chemotherapy does not convincingly improve the survival of young patients, in whom peritoneal metastasis is observed more frequently[20]. A positive impact on survival by combined intraperitoneal chemotherapy has been reported in advanced gastric cancer when used as an adjuvant treatment[21–23]. Because of the apparently beneficial effect of chemotherapy administered locally to the potential site of tumour progression[24], intraperitoneal chemotherapy was given after palliative resection on the assumption that this approach might at least delay disease progression, and hopefully prolong survival.

In an attempt to increase the treatment efficacy of intraperitoneal chemotherapy, this study focused on patients with a small tumour burden, with the aim of optimizing the regimen, timing and technique of chemotherapy[9]. Maximal cytoreductive surgery was performed to reduce tumour bulk in an effort to overcome the limited penetration of drugs into the tissue[5]. To standardize these procedures, one designated surgical team undertook all the operations. The combination of cisplatin and 5-FU with a 51 per cent response rate was considered to be the appropriate regimen, even though it does not improve survival[25,26]. The intraperitoneal administration of this regimen also had acceptable toxicity in a phase I trial[13]. The first dose of chemotherapy was started as early as possible (day 1 after operation) from a tumour kinetic standpoint[27]. Considering the fact that an increase in the permeability-area product reflected an increase in the effective peritoneal surface area[28], total intraperitoneal volume was adjusted by as much as 2000 ml, but it was difficult to infuse more than 3000 ml into the peritoneal cavity because of severe distending pain in these patients.

Although disease progression was not confirmed by autopsy in any patient, the pattern of disease progression was mostly intra-abdominal (carcinomatosis). Survival in this study was comparable to that reported by Terashima *et al.*[29], who noted a median survival time of 343 days with overt peritoneal metastasis (P_{2-3}). They used intraperitoneal cisplatin and intravenous 5-FU infusion. The survival effect of the present study, if any, could be attributed to combined cytoreductive surgery and intraperitoneal chemotherapy, considering the doubling time of the residual tumour.

Several factors could account for this modest result. Most randomized reports advocating the role of intraperitoneal chemotherapy have utilized a hyperthermic technique[30,31]. The principal drawback of the present trial seems to be a mechanical one. The resection might unavoidably have left gross residual tumour behind, and drug penetration might therefore have been inadequate. Loggie *et al.*[32] proved this hypothesis by performing cytoreductive surgery and intraperitoneal hyperthermic chemotherapy. A significant difference in survival between R_0/R_1 *versus* R_2 resection status was seen (28 or more *versus* 10 months). A second factor relates to the long-term use of Tenckhoff catheters, which fail to provide uniform drug delivery because of a natural fibrotic reaction to the plastic catheter. In addition, many chemotherapeutic agents have a sclerotic effect on the peritoneum. These factors, together with the adhesive effects of surgery itself, may cause uneven and inefficient drug delivery[19].

Although the planned dosage in this study was small compared with the clinically recommended dose[12,33], half of the courses were postponed owing to toxicity. Neither of the chemotherapeutic agents used in this protocol could achieve adequate dose intensity. The dose intensity of cisplatin was only 63 per cent. In contrast to the results reported by Sautner *et al.*[34], bone marrow suppression was the most predominant toxic effect. This toxicity profile was similar to that of Terashima *et al.*[29]. Such profiles indicate that chemotherapeutic agents enter the systemic circulation even in the presence of gross residual peritoneal disease.

Several conclusions can be drawn from from these results. First, quantification of intra-abdominal seeding is important. Patients in whom complete cytoreduction cannot be achieved, such those with distant nodal metastasis and large peritoneal implants, should not receive chemotherapy. Performance status also emerges as a major determining factor for patient selection. Patients in whom treatment was interrupted in this study underwent a similar adverse clinical course to that of patients whose disease progressed (data not shown). Second, it may not be appropriate to use a Tenckhoff catheter repeatedly[34,35]. Systemic therapy following or combined with intraperitoneal chemotherapy might be an alternative approach. Third, adequate dose adjustment is necessary. To enhance the dose intensity of cisplatin, the thiosulphate rescue may be considered[32]. Based on these results, further phase II trials should be conducted to determine the role of intraperitoneal chemotherapy for gastric cancer with intra-abdominal seeding.

Acknowledgements

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Original article

Postoperative body-weight loss and survival after curative resection for gastric cancer

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Background: Body-weight loss has been reported as a poor prognostic factor for some malignancies. The purpose of this study was to evaluate the prognostic value of postoperative body-weight loss in patients with gastric cancer.

Methods: In 564 patients who underwent curative resection for gastric cancer, usual body-weight, body-weight at the time of resection and that 6 and 12 months after resection were recorded prospectively.

Results: The 5-year survival rate of patients who lost more than 5 per cent of their 6-month postoperative weight by 12 months after resection was 63 per cent while that of patients who maintained 95 per cent or more of their 6-month postoperative weight was 84 per cent ($P < 0\cdot001$). Multivariate analysis revealed that serosal invasion, nodal metastasis, body-weight loss during the second 6-month interval after resection and extent of gastric resection were independent prognostic indicators.

Conclusion: When a patient loses body-weight during the second 6-month interval after curative resection for gastric cancer, recurrent disease should be suspected.

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Introduction

Prognostic factors in cancer serve to predict clinical outcome for individual patients and are particularly useful in identification of subgroups at high risk of relapse. There is general consensus that the anatomical extent of gastric cancer is an independent prognostic variable. This has been shown for depth of tumour invasion, involvement of regional lymph nodes and presence of distant metastasis[1]. However, there is no consensus on the importance of patient-related variables as independent factors determining survival[2].

Body-weight loss is reported to be a poor prognostic factor in lung cancer[3], oesophageal cancer[4] and colorectal cancer[5]. Survival is affected negatively if a patient with gastric cancer has greater than 10 per cent weight loss[6]. In one study, weight less than 90 per cent of ideal body-weight, 10 per cent weight loss over the preceeding 6 months, or both were associated with a poor prognosis[7].

Patients with cancer should be followed by the primary treatment team after curative treatment to find potentially curable recurrences, to palliate symptomatic recurrences, and to identify and resolve treatment-related problems[8]. Follow-up of patients with gastric cancer after curative resection consists of a careful history and physical examination followed by radiological and laboratory studies.

Curative surgical resection of malignancy is usually associated with a return of normal food intake and normal body-weight[9], except in gastric cancer[10]. The aim of this study was to measure body-weight of patients with gastric cancer regularly in order to identify whether postoperative body-weight loss is of similar prognostic value to preoperative weight loss.

Patients and methods

Some 672 patients underwent curative resection for gastric cancer from 1992 to 1996. The definition of curative resection fulfilled criteria provided by the Korean Gastric Cancer Association[11]. However, patients with stage IV gastric cancer were excluded from the study. Fifty-two patients, including eight who died after operation, died within 1 year of resection. Fifty-six patients did not return for follow-up against recommendation. Usual body-weight, body-weight at the time of resection, and that at 6 and

12 months after resection were recorded prospectively in the remaining 564 patients. There were 364 men and 200 women, of median age 57 years. According to the tumour node metastasis classification (Union Internacional Contra la Cancrum, 1997)[1], 158 patients had stage IA, 152 stage IB, 102 stage II, 88 stage IIIA and 64 stage IIIB.

A preliminary analysis revealed that patients who died during the third 6-month interval after resection lost a mean of 5 per cent of postoperative 6-month body-weight during the second 6-month interval. Patients were therefore classified into subgroups according to body-weight loss: patients in group 1 ($n = 479$) maintained 95 per cent or more of their 6-month postoperative body-weight 12 months after resection and those in group 2 ($n = 85$) lost more than 5 per cent of their 6-month postoperative weight at 12 months after resection.

Survival was calculated from the date of resection until cancer-related death or last date of follow-up. Kaplan–Meier survival curves were plotted and compared using the log rank test. A multivariate analysis was performed using the Cox proportional hazards model. Other statistical methods were Student's t test and Pearson correlation. $P < 0{\cdot}05$ was considered significant.

Results

Body-weight

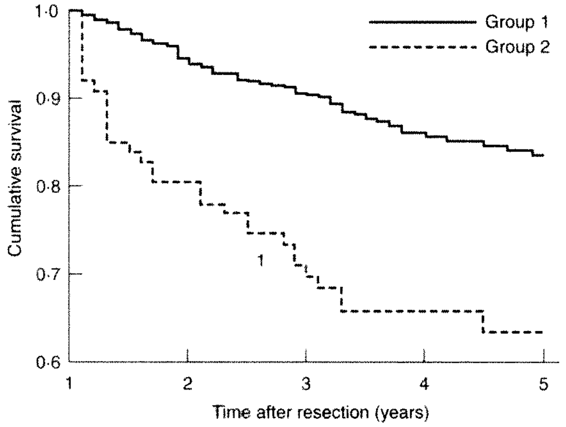
Mean(s.d.) body-weights of patients who died from recurrent cancer ($n = 107$) were significantly lower at all timepoints than those of living patients or patients who died from a non-cancer-related illness: preoperative body-weight, 56·8(8·4) and 59·1(9·4) kg ($P = 0{\cdot}02$); body-weight at 6 months after resection, 51·3(7·5) and 54·0(8·7) kg ($P < 0{\cdot}01$); body-weight at 12 months after resection, 50·4(7·8) and 54·3(8·6) kg ($P < 0{\cdot}01$) respectively.

Preoperative body-weight loss

Mean(s.d.) body-weight at the time of resection was 96(5) per cent of usual body-weight. Preoperative body-weight loss correlated with stage of gastric cancer ($r = -0{\cdot}17$, $P < 0{\cdot}01$).

Postoperative body-weight loss

Body-weight loss during the first 6-month interval after resection did not correlate with stage of gastric cancer ($r = -0{\cdot}04$, $P = 0{\cdot}36$). Body-weight was stable during the second 6-month interval in most patients (85 per cent). However, body-weight loss during the second 6-month interval after resection showed a trend toward correlation with preoperative stage of gastric cancer, although this was not statistically significant ($r = -0{\cdot}08$, $P = 0{\cdot}07$).



No. at risk					
Group 1	479	442	416	321	227
Group 2	85	68	56	49	27

Fig. 1 Survival distribution of patients according to weight loss during the second 6-month interval after resection. Patients in group 1 maintained 95 per cent or more of 6-month post-operative body-weight and those in group 2 lost more than 5 per cent of 6-month postoperative weight by 12 months after resection. $P < 0{\cdot}001$ (log rank test)

Postoperative body-weight loss and prognosis

Mean(s.d.) duration of follow-up was 4·5(1·7) years. Twenty-four (4 per cent) of patients were lost to follow-up. Body-weight loss during the first 6-month interval did not correlate with prognosis ($r = -0{\cdot}06$, $P = 0{\cdot}17$); however, that during the second 6-month interval did correlate with prognosis ($r = 0{\cdot}14$, $P < 0{\cdot}01$). The 5-year survival rate in group 1 was 84 per cent and that in group 2 was 63 per cent ($P < 0{\cdot}001$) (*Fig. 1*).

Other prognostic factors

The relationships between clinicopathological factors and survival are given in *Table 1*. Serosal invasion, lymph node metastasis, extent of gastric resection, body-weight loss during the second 6-month interval after resection, adjuvant chemotherapy and preoperative body-weight loss were significant factors on univariate analysis. Multivariate analysis by Cox proportional hazards model revealed that body-weight loss during the second 6-month interval after resection, serosal invasion, lymph node metastasis and extent of gastric resection were significant prognostic factors among six significant variables on univariate analysis (*Table 2*).

Table 1 Summary of univariate analyses

	No. of patients	5-year survival rate (%)	*P*
Serosal invasion			< 0·001
No	423	89	
Yes	141	55	
Lymph node metastasis			< 0·001
No	350	92	
Yes	214	62	
Extent of gastric resection			< 0·001
Subtotal	423	87	
Total	141	62	
Weight loss during the second 6 months after resection			< 0·001
No	479	84	
Yes	85	63	
Adjuvant chemotherapy			< 0·001
No	437	84	
Yes	127	69	
Preoperative weight loss			0·001
No	386	84	
Yes	178	73	
Lymph node dissection			0·168
Standard	239	83	
Extended	325	79	
Weight loss during the first 6 months after resection			0·384
No	181	82	
Yes	383	80	
Gender			0·912
Women	200	79	
Men	364	81	

Table 2 Cox proportional hazards model with clinicopathological factors

Variable	Coefficient	s.e.	*P*	Risk ratio
Weight loss*	1·03	0·22	< 0·001	2·80 (1·82, 4·28)
Serosal invasion	− 0·99	0·21	< 0·001	0·37 (0·25, 0·56)
Nodal metastasis	− 1·32	0·23	< 0·001	0·27 (0·17, 0·42)
Gastric resection	− 0·80	0·20	< 0·001	0·45 (0·30, 0·66)

Values in parentheses are 95 per cent confidence intervals. *During second 6-month interval after resection

Discussion

Nutritional status has gained greater attention as a surgical risk factor in recent years. There is evidence that cancer is frequently associated with malnutrition and that this is particularly evident when the gastrointestinal tract is involved[12]. One indirect way of estimating nutritional intake is to record body-weight[13] and body-weight change can easily be identified by serial weight measurements.

Preoperative body-weight loss is commonly seen in gastric cancer. In a study by Dewys *et al.*[6], 83 per cent of patients with gastric cancer had a decrease in body-weight of more than 10 per cent. In this study, body-weight loss became more severe with the progression of gastric cancer. The poor prognosis of patients with preoperative body-weight loss can be explained by the correlation of preoperative body-weight loss with stage of gastric cancer.

The causes of body-weight loss in patients with cancer are multifactorial and include cancer-related decreased food intake, local obstruction, abnormal swallowing, maldigestion and malabsorption resulting from obstruction of biliary or pancreatic secretions, and increased basal energy expenditure with alterations in carbohydrate, protein and lipid metabolism[14]. Unlike in starvation, body-weight loss in cancer arises equally from loss of muscle and fat, and the process is characterized by an increased catabolism of skeletal muscle and a decrease in protein synthesis[15]. Hepatic protein synthesis is impaired in patients with gastric cancer, and patients with preoperative body-weight loss have lower rates of hepatic protein synthesis than those without weight loss[16]. The increased rate of fat oxidation seems to be another example of deranged metabolism in patients with cancer[17].

The degree of body-weight loss after gastrectomy depends on the extent of gastric resection and method of reconstruction; patients infrequently regain preoperative body-weight[10] because of a lower calorie intake after gastric resection[18]. Moreover, recurrence of gastric cancer is not infrequent even after curative resection[19]. When gastric cancer recurs, body-weight decreases as a result of diminished nutrient intake, increased nutrient losses and tumour-induced derangements in host metabolism.

In contrast to the association between preoperative body-weight loss and stage of gastric cancer, loss of body-weight during the first 6-month interval after curative resection did not correlate with stage of gastric cancer. Body-weight of most patients was stable during the second 6-month interval after resection. However, 15 per cent of patients lost more than 5 per cent of their 6-month postoperative weight during the following 6 months and the prognosis of these patients was worse than that of their weight-stable counterparts. This body-weight loss should be regarded as a marker of recurrence, an observation confirmed by multivariate analysis. Such weight loss may therefore reflect recurrence of cancer and of cancer cachexia, regardless of stage of gastric cancer at resection. Preoperative body-weight loss cannot be used as an independent prognostic factor[20] because of its association with tumour stage.

Periodic measurement of body-weight as well as a careful history and physical examination followed by appropriate radiological and laboratory studies should be performed during follow-up for patients with gastric cancer after curative resection. When a patient loses body-weight during the second 6-month period after resection, recurrence should be carefully sought and appropriate therapy given.

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Original article

Impact of diagnostic laparoscopy on the management of gastric cancer: prospective study of 120 consecutive patients with primary gastric adenocarcinoma

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Background: Peritoneal seeding or liver metastases found at laparotomy usually preclude curative treatment in patients with gastric adenocarcinoma. Such exploratory laparotomies may be avoided by diagnostic laparoscopy. However, routine diagnostic laparoscopy does not benefit those patients who proceed to laparotomy after negative laparoscopy. The aim of this study was to evaluate prospectively the selective use of laparoscopy in uncertain situations.

Methods: One hundred and twenty consecutive patients with primary gastric adenocarcinoma were studied prospectively. Diagnostic laparoscopy was performed in patients with clinical T_4 tumours or suspected metastases, unless laparotomy was required for symptomatic disease.

Results: Ninety-six of 120 patients were selected for immediate laparotomy with curative intent ($n = 81$) or for palliation ($n = 15$). In two of the 81 patients gastrectomy was abandoned because of unexpected peritoneal carcinomatosis. Fifteen patients underwent diagnostic laparoscopy, which identified intra-abdominal metastases in six; the other nine patients proceeded to laparotomy, which revealed peritoneal metastases not detected at laparoscopy in four patients. The remaining nine patients had overt metastases and were referred for systemic chemotherapy without abdominal exploration.

Conclusion: Diagnostic laparoscopy in selected patients effectively limits the number of unnecessary invasive staging procedures. Routine use of diagnostic laparoscopy in all patients with gastric adenocarcinoma is not warranted.

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Introduction

Selection of the appropriate treatment for gastric cancer requires accurate tumour staging. The clinical staging of patients with gastric cancer can be improved by laparoscopy, since it may identify intra-abdominal tumour deposits in lymph nodes, the liver or on peritoneal surfaces, which are not detectable by non-invasive imaging[1,2]. Staging laparoscopy has therefore been recommended for all patients with gastric cancer considered for potentially curative gastrectomy[3,4]. More precise clinical staging does not, however, benefit individual patients unless it results in either more effective or less invasive treatment. The routine use of staging laparoscopy in patients with gastric cancer has therefore been questioned[5].

Diagnostic laparoscopy has been advocated to select patients for neoadjuvant therapy as in European Organisation for Research on Treatment of Cancer protocol 40954[6]. However, neither neoadjuvant radiotherapy nor chemotherapy[7–9] is currently accepted as standard treatment for gastric cancer. Alternatively, diagnostic laparoscopy can be used to identify patients with intra-abdominal tumour deposits not detected by preoperative imaging and which preclude curative treatment. Patients with incurable disease found at laparoscopy may be spared an exploratory laparotomy. Such patients are currently the only ones to benefit from diagnostic laparoscopy.

The majority of patients with gastric cancer, however, will undergo laparotomy for gastrectomy with either curative intent or for palliation. This group also does not benefit from diagnostic laparoscopy. Moreover, some caution has been voiced because even minimally invasive procedures, especially those performed separately and under general anaesthesia, inflict surgical trauma with associated morbidity and mortality[5]. In addition, the long-term effects of procedure-related immunosuppression in a patient who will later undergo potentially curable gastrectomy are not known.

To define better the current role of diagnostic laparoscopy in the management of patients with gastric cancer the authors have implemented an algorithm, in which diagnostic laparoscopy is used selectively in uncertain situations, and prospectively evaluated all patients with a diagnosis of gastric adenocarcinoma.

Patients and methods

Between June 1999 and July 2001 all patients with a histologically confirmed diagnosis of primary gastric adenocarcinoma admitted to the Department of Surgery, University of Heidelberg, were evaluated prospectively regarding the indication for diagnostic laparoscopy. Patients with recurrent disease, gastric lymphoma or sarcoma were excluded. The diagnostic assessments included endoscopy, endosonography, abdominal ultrasonography and computed tomography or magnetic resonance imaging as appropriate to identify metastases or local infiltration.

Immediate laparotomy was performed in patients with symptomatic disease (obstruction, bleeding, perforation) and in asymptomatic patients without evidence of distant metastases or locally advanced tumour that would preclude potentially curative gastrectomy (*Fig. 1*). Patients with distant metastases were referred for systemic chemotherapy, unless symptomatic disease (e.g. obstruction, bleeding) required palliative gastrectomy or bypass. Laparoscopy was performed in asymptomatic patients eligible for potentially curative gastrectomy, if preoperative imaging and endoscopy were inconclusive regarding local resectability (clinical T3/clinical T4) or the presence or absence of peritoneal carcinomatosis or liver metastases.

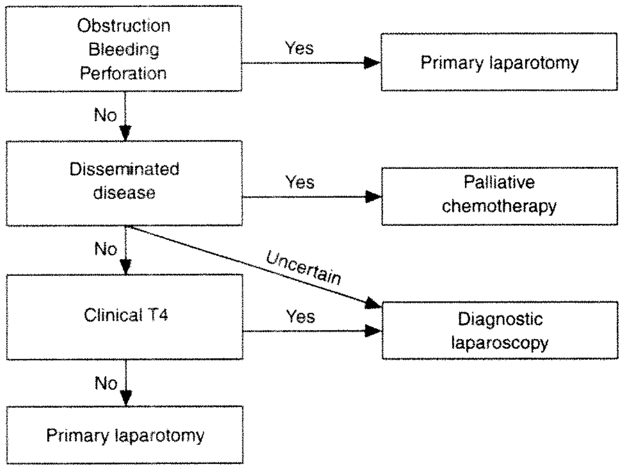

Fig. 1 Diagnostic and treatment algorithm for gastric adenocarcinoma

Laparoscopy was performed under general anaesthesia using a 0° or 30° instrument at the discretion of the attending surgeon immediately before laparotomy. The patient was positioned as for an open upper abdominal procedure and the operating table was repositioned according to the intra-abdominal region to be inspected. A thorough inspection of all four quadrants of the peritoneal cavity was performed and frozen sections were taken from any tissue suspected to be tumour. The lesser sac was not inspected routinely[4] as this provided useful diagnostic information in only 10 per cent of patients undergoing diagnostic laparoscopy[2], while six of 14 instances of retroperitoneal invasion were missed in another study of laparoscopic exploration of the lesser sac[10].

Results

Between June 1999 and July 2001 a total of 120 consecutive patients with a histologically proven primary gastric adenocarcinoma were evaluated prospectively for diagnostic laparoscopy. The median age of the 78 men and 42 women was 65 (range 30–84) years. During the study three patients presented with bleeding. No patient presented with perforation of gastric cancer. All procedures were performed electively.

Abdominal imaging revealed extensive liver metastases in nine patients without signs of gastric obstruction. They were referred for systemic chemotherapy without abdominal exploration.

Primary laparotomy with curative intent was performed in 81 patients without evidence of distant metastases or locally advanced disease. A potentially curative gastrectomy with D_2 lymphadenectomy (R0) was accomplished in 77 (95 per cent) of the 81 patients. Histological examination revealed microscopic tumour infiltration at the resection margin in two patients (R1) and in two other patients unexpected peritoneal carcinomatosis was found that involved the left diaphragm and the greater omentum in one each. Fifteen patients underwent primary laparotomy for palliation.

Primary laparoscopy was performed in 15 patients with an inconclusive preoperative diagnosis regarding the presence or absence of liver metastases, peritoneal carcinomatosis or local infiltration. These patients were otherwise eligible for potentially curative gastrectomy. Laparoscopy was uneventful in all patients and there were

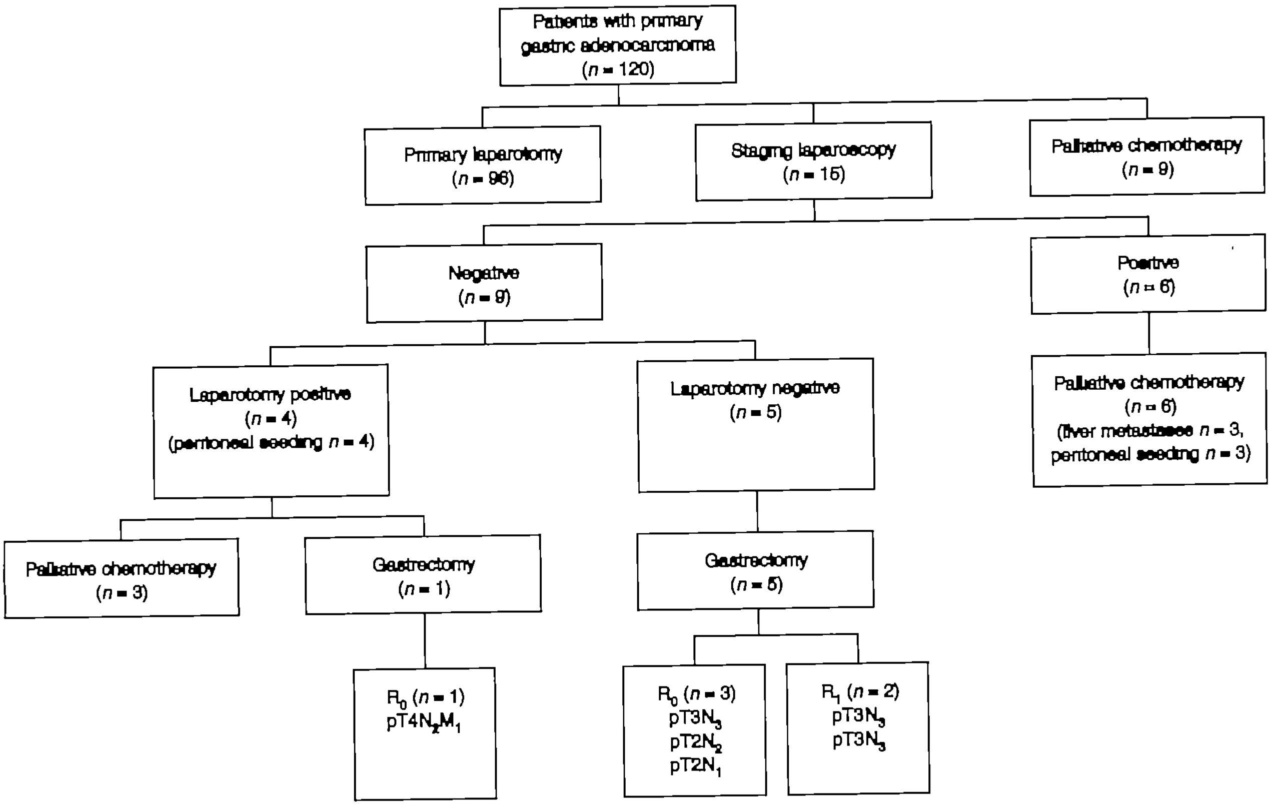
Patients with primary gastric adenocarcinoma (n = 120)
Primary laparotomy (n = 96)
Staging laparoscopy (n = 15)
Palliative chemotherapy (n = 9)
Negative (n = 9)
Positive (n = 6)
Laparotomy positive (n = 4) (peritoneal seeding n = 4)
Laparotomy negative (n = 5)
Palliative chemotherapy (n = 6) (liver metastases n = 3, peritoneal seeding n = 3)
Palliative chemotherapy (n = 3)
Gastrectomy (n = 1)
Gastrectomy (n = 5)
R_0 (n = 1) $pT4N_xM_1$
R_0 (n = 3) $pT3N_3$ $pT2N_2$ $pT2N_1$
R_1 (n = 2) $pT3N_3$ $pT3N_3$

Fig. 2 Use of diagnostic laparoscopy in 120 patients with gastric adenocarcinoma. pTNM, pathological tumour node metastasis

no procedure-related complications. In six of the 15 patients previously unconfirmed liver metastases or peritoneal seeding were found and gastrectomy was abandoned (*Fig. 2*). In the other nine patients laparoscopy indicated resectable tumour. They went on to laparotomy for a potentially curative operation and therefore had no benefit from laparoscopy. At subsequent laparotomy, four of the nine patients thought to be candidates for a curative operation had small intraperitoneal tumour deposits and no resection was performed in three. One patient had a 3-mm tumour deposit on the presacral peritoneum, which had not been discovered at laparoscopy. As the biopsy taken for intraoperative frozen section had removed all visible peritoneal tumour, a potentially curative gastrectomy was performed. After an uneventful postoperative course this patient died 4 months later from recurrent disease. Two patients had tumour deposits on the greater omentum (n = 2) and a third had deposits on the retroperitoneal surface. Only four of the 15 patients selected for laparoscopy eventually had a potentially curative (R0) operation (*Fig. 2*).

All nine patients in whom findings at laparoscopy or laparotomy prompted palliative chemotherapy without gastrectomy were followed to determine the need for subsequent surgical intervention. At a median age of 68 (range 60–72) years peritoneal carcinomatosis or liver metastases had precluded curative surgery in six and three patients respectively. At the time of this report four patients with peritoneal seeding have died after a median of 37 weeks (follow-up 15–50 weeks) and two are alive with disease at 4 and 7 weeks. All three patients with liver metastases are still alive at a median of 38 (range 33–51) weeks. None of the nine patients has required laparotomy at a later stage.

Discussion

This is the first study to evaluate prospectively the use of selective staging laparoscopy in a consecutive series of all patients seen with gastric cancer. It is generally agreed that laparoscopy allows more accurate clinical staging than noninvasive imaging. The procedure is well tolerated and the immediate complication rate is low, ranging from 0 to 3 per cent[1–3,11]. Laparoscopic findings may cause a change of treatment in a number of patients. However, the same findings would have been made at laparotomy. Since neoadjuvant therapy for gastric cancer is still experimental, a true benefit from laparoscopy accrues only for patients with incurable disease and then only if a subsequent laparotomy can be avoided.

Few studies have specifically addressed this critical issue. In a non-consecutive series between 1990 and 1995, 15 per cent of all patients operated on for gastric cancer underwent diagnostic laparoscopy. As a result laparotomy was avoided in 24 (23 per cent) of 103 patients[12] and 79 laparoscopies (77 per cent) were followed by laparotomy. Peritoneal metastases were identified laparoscopically in 15 (22 per cent) of 69 patients with disease initially deemed resectable in a study performed from 1991 to 1995 and laparotomy was subsequently abandoned[3]. The authors advocated staging laparoscopy for all patients with potentially resectable gastric cancer, although the benefit for the 54 patients (78 per cent) who proceeded to laparotomy was unclear. In a study that evaluated patients with contrast-enhanced computed tomography and ultrasonography between 1992 and 1995, 76 consecutive patients with gastric adenocarcinoma considered resectable underwent diagnostic laparoscopy. Despite apparently extensive preoperative assessment, laparotomy was abandoned in 41 per cent of patients after laparoscopic staging[10].

In a more recent study conducted between 1994 and 1998, laparoscopy obviated the need for laparotomy in 18 (19 per cent) of 93 patients with potentially resectable oesophagogastric carcinoma. Additional laparoscopic ultrasonography identified another eight patients, in whom laparotomy was avoided[13]. The detection of otherwise occult metastases by laparoscopic ultrasonography similarly precluded laparotomy in four of 20 patients with cancer of the cardia scheduled for resection[14]. However, the value of laparoscopic ultrasonography is not easily determined. Only three (3 per cent) of 107 consecutive patients with gastric cancer in one series were upstaged by laparoscopic ultrasonography[2], and in another study of selected patients it detected additional metastatic disease in eight (11 per cent) of 75 patients[11]. Neither study reported the impact of laparoscopic ultrasonography on the decision to perform laparotomy. This issue was addressed only in a small series of 18 patients with carcinoma of the cardia involving the oesophagus[15]. Laparoscopy in combination with laparoscopic ultrasonography avoided laparotomy in two of 18 patients, but the contribution of the ultrasonographic examination to the final treatment decision remains unclear.

It appears from these studies that the majority of patients go on to laparotomy after laparoscopy and have no apparent benefit from laparoscopy[2,3,10,13–16]. The potential risks of laparoscopy therefore need to be reconsidered. Quite apart from the relatively low immediate mortality and morbidity[5], there may be a long-term risk in patients with cancer. Staging laparoscopy is usually performed with pneumoperitoneum and general anaesthesia, and may be prolonged (up to 66–75 min), especially if endoscopic ultrasonography is included[12,16]. It is frequently performed as a separate procedure, with gastrectomy following within 2–3 weeks in patients with potentially curable disease[2,12,15,17]. Liberal use of even minimally invasive procedures should raise some concern in these patients, because little is known about the long-term effects of staging laparoscopy on the course of malignant disease in humans. Animal studies provide ample evidence that pneumoperitoneum impairs cellular[18] and humoral[19] immune responses and promotes tumour growth[20–24]. Similar considerations may apply to patients with gastric cancer. The effect of laparoscopy on the human immune system has been compared with that of open surgery in several randomized trials. All trials documented profound effects of laparoscopy on both the cellular[25] and the humoral[26] immune response compared with the preoperative immune status, and in some studies the effects of laparoscopy were no different from those of laparotomy[26–28]. Since the immunosuppression resulting from laparoscopic procedures could favour metastatic growth, the advantages of staging laparoscopy should be balanced carefully against the potential risks.

Using laparoscopy selectively, in the present study six patients with incurable tumour of 15 patients undergoing laparoscopy had a benefit, while 77 (95 per cent) of 81 patients undergoing primary laparotomy for curative gastrectomy had a successfully completed procedure. Laparoscopy should be reserved for patients with an increased risk of local irresectability or intra-abdominal metastases.

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Original article

Results of laparoscopic Nissen fundoplication at 2–8 years after surgery

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Background: Although the long-term results of open fundoplication for gastro-oesophageal reflux disease are well documented, there have been few reports of the long-term results of laparoscopic fundoplication.

Methods: Between January 1993 and July 1999, 179 consecutive patients underwent laparoscopic floppy Nissen fundoplication. Of these, 175 were available for long-term follow-up. Structured symptom questionnaires were completed by 140 patients (80 per cent) at 2–5 years (n = 92) or 5–8 years (n = 48) after operation.

Results: Patient satisfaction with surgery was 91 per cent at a median follow-up of 48 (range 24–99) months. Visick scores of I or II were recorded by 84 per cent. Ninety per cent of patients remained free from significant reflux symptoms. Side-effects were common (22 per cent) but rarely affected patient satisfaction. Of the 19 patients (14 per cent) taking regular antireflux medication, eight used it for non-reflux symptoms and 12 had normal postoperative pH tests.

Conclusion: Laparoscopic floppy Nissen fundoplication is an effective and durable treatment for gastro-oesophageal reflux disease. Longer-term follow-up of patients operated on beyond the learning curve can be expected to show further improvements in surgical outcome.

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Introduction

Laparoscopic fundoplication for gastro-oesophageal reflux disease (GORD) was first reported in 1991[1,2]. Since then it has gained widespread acceptance as the technique of choice in the surgical treatment of GORD. Short-term results of laparoscopic antireflux surgery are equivalent to those of the open approach[3–6] but information on longer-term outcome is required to confirm its durability. This study reports on the longer-term outcome of laparoscopic floppy Nissen fundoplication in a consecutive series of patients operated on by a single surgeon in a district general hospital.

Patients and methods

Between January 1993 and July 1999, 179 consecutive patients underwent laparoscopic floppy Nissen fundoplication for symptomatic gastro-oesophageal reflux disease. This figure includes all patients operated on from the introduction of the laparoscopic technique until July 1999, and thus incorporates the learning curve experience. The 12 patients (7 per cent) who required conversion to an open procedure, mainly early in the series, were included in the overall analysis on an intention-to-treat basis. The median age of the patients was 41 (range 9–82) years; 118 (66 per cent) were male. All operations were performed or supervised by a single surgeon. All data were collected prospectively.

Preoperative investigations

Patient symptom information was obtained using a standardized symptom questionnaire, which included a DeMeester Symptom Score[7], details of symptom duration and medication taken to relieve reflux symptoms.

All patients underwent outpatient upper gastrointestinal endoscopy. Oesophagitis was scored using the classification of Savary and Miller[8]. Thirty-six (20 per cent) had erosive oesophagitis (grade 2 or higher) and 19 (11 per cent) had Barrett's oesophagus.

Twenty-four-hour ambulatory oesophageal pH monitoring was performed before operation in all patients. From 1996 all patients underwent standard oesophageal manometry. Before this the pull-back technique was used to determine the proximal border of the lower oesophageal sphincter for 24-h pH monitoring[9]. The techniques used for oesophageal manometry and 24-h pH monitoring have been described in detail previously[10].

Operative technique

Laparoscopic floppy Nissen fundoplication was performed by fashioning a floppy 360° posterior wrap over a 56-Fr oesophageal bougie, with routine division of the short gastric vessels. A 2-cm wrap was created with three non-absorbable sutures, the proximal two of which included the anterior oesophageal wall. The completed wrap was anchored to the right pillar of the crus with a further non-absorbable suture. Initially silk sutures were used. In June 1997, after 95 operations, the suture material changed to braided polyester (Ethibond®; Ethicon, Edinburgh, UK). Crural repair was performed selectively for the first 80 patients, after which it was performed routinely.

Postoperative assessment

Follow-up was performed at 6 weeks, 6 months and 1 year after operation by independent nurse practitioner review using a structured symptom questionnaire. Patients were asked to grade the following symptoms on a four-point scale (0, absent; 1, mild; 2, moderate; 3, severe): heartburn, regurgitation, dysphagia, epigastric pain, postprandial dizziness/faintness, postprandial bloating, restriction of belching and abdominal pain. The DeMeester Symptom Score (minimum 0, maximum 9) was derived from the first three symptoms. In addition, patients were asked about the presence of chest tightness or discomfort on eating, the ability to relieve bloated feelings by belching, the ability to vomit, the presence of increased passage of flatus (none, mild, marked) and the presence of persistent diarrhoea. Finally they were asked to complete a modified Visick grading[11]. Twenty-four-hour pH tests were performed at 6 months and upper gastrointestinal endoscopy 1 year after operation.

Longer-term follow-up was performed in all patients by postal survey, incorporating the same structured symptom questionnaire and modified Visick grade applied at the early postoperative assessment points. Patients were asked (1) whether antireflux surgery had improved their reflux symptoms; (2) whether antireflux surgery had resulted in any new, troublesome symptoms; and (3) if they felt satisfied with the overall result of their operation.

Statistical analysis

Patients were divided into two groups based on the length of available follow-up. In group 1 follow-up ranged between 2 and 5 years (median 36 months); in group 2 follow-up was between 5 and 8 years (median 74 months). Non-parametric paired data sets were analysed using Wilcoxon's signed rank test. Differences in proportions were analysed using a χ^2 test with Yates' correction for continuity. A commercially available statistical software package (Sigmastat 2.03®; SPSS, Chicago, Illinois, USA) was used for all statistical analysis.

Results

There were no deaths related to surgery. Twelve patients (7 per cent) required conversion to an open procedure, seven within the first 50 cases of the series, three among cases 51–100 and two among cases 100–150. Two patients have died from causes unrelated to the antireflux surgery. A further two patients underwent oesophageal resection, one for adenocarcinoma *in situ* and one for an oesophageal leiomyosarcoma. These four patients were excluded from the long-term follow-up of symptoms. The remaining 175 patients were available for longer-term follow-up of at least 24 months following surgery. Of these, 140 (80 per cent) returned the postal questionnaire. The response rate was 88 per cent (92 of 105) in group 1 and 69 per cent (48 of 70) in group 2. Paired short-term and longer-term follow-up data were available for 136 (97 per cent) of the responders, 92 (100 per cent) in group 1 and 44 (92 per cent) in group 2. Mean length of follow-up was 48 (range 24–99) months. *Table 1* shows the modified Visick grades for all responders at short-term and longer-term follow-up points.

Patient satisfaction with the operation was 91 per cent overall (95 per cent in group 1 and 85 per cent in group 2). If patients whose operation was converted to an open procedure were excluded, the respective satisfaction rates were 95, 94 and 95 per cent. Overall, 90 per cent of patients were free from significant reflux symptoms, i.e. scores for heartburn and regurgitation were 1 or less (91 per cent in

Table 1 Postoperative modified Visick grades of patients undergoing laparoscopic Nissen fundoplication for gastro-oesophageal reflux disease

	Time after operation		
Visick grade	1 year	2–5 years	> 5 years
I	101 (58)	26 (28)	13 (27)
II	58 (33)	54 (59)	25 (52)
III	12 (7)	12 (13)	8 (17)
IV	4 (2)	0 (0)	2 (4)
Total	175	92	48

Values in parentheses are percentages

Table 2 Change in symptoms after Nissen fundoplication

	Before operation	1 year after operation			2–8 years after operation		
		Improved*	Unchanged	Worsened	Improved*	Unchanged	Worsened
Heartburn	135	130 (96)	4 (3)	1 (1)	119 (93)	8 (6)	1 (1)
Regurgitation	141	134 (95)	7 (5)	0 (0)	117 (91)	8 (6)	4 (3)
Dysphagia	68	59 (87)	8 (12)	1 (1)	47 (76)	14 (23)	1 (2)

Values in parentheses are percentages. *Or abolished

Table 3 Adverse symptoms or side-effects before and at long-term follow-up after laparoscopic Nissen fundoplication for gastro-oesophageal reflux disease

	Before operation (n = 140)	After operation: Overall (n = 140)	Group 1 (n = 92)	Group 2 (n = 48)
Abdominal pain*	–	18 (13)	12 (13)	6 (12)
Epigastric pain*	68 (49)	13 (9)†	7 (8)	6 (12)
Postprandial dizziness*	–	8 (6)	5 (5)	3 (6)
Postprandial bloating*	81 (58)	47 (34)†	30 (33)	17 (35)
Inability to relieve bloating by belching	–	35 of 47 (74)	23 of 30 (77)	12 of 17 (71)
Restriction of belching*	–	35 (25)	27 (29)	8 (17)
Chest discomfort on eating	40 (29)	21(15)†	14 (15)	7 (15)
Odynophagia	83 (59)	19 (14)†	10 (11)	9 (19)
Marked increase in flatus	–	69 (49)	51 (55)	18 (38)
Persistent diarrhoea	–	22 (16)	15 (16)	7 (15)

Values in parentheses are percentages. *Moderate or severe symptoms (2 or 3 on symptom severity scale). †$P < 0{\cdot}01$ *versus* before operation (χ^2 test)

group 1; 87 per cent in group 2). Compared with preoperative symptom scores, heartburn was abolished or improved in 96 per cent of patients at 1 year after operation, and was unchanged or worse in 4 per cent (*Table 2*). At longer-term follow-up heartburn was abolished or improved in 93 per cent of patients. Similar figures were seen for regurgitation, which was abolished or improved in 95 per cent of patients at 1 year and 91 per cent at longer-term follow-up. Preoperative dysphagia was abolished or improved in 87 per cent of patients at 1 year after fundoplication, and in 76 per cent at longer-term follow-up.

Table 3 shows the numbers of patients reporting adverse symptoms or side-effects before and after surgery. Symptoms of epigastric pain, postprandial bloating, chest discomfort on eating and odynophagia were common before operation, and were significantly reduced by fundoplication. Although 22 per cent of patients answered 'Yes' in response to the question 'Have you had any troublesome side-effects from your operation?', most felt that these were minor in comparison to the improvement in reflux symptoms. Only 6 per cent of patients reported side-effects combined with dissatisfaction with the results of surgery.

Analysis of the paired symptom scores at 1 year and either 2–5 years or 5–8 years after fundoplication revealed a statistically significant worsening of certain symptoms with time from surgery. DeMeester Symptom Scores (median (interquartile range) 0 (0–1) *versus* 0 (0–2)) and abdominal pain scores (0 (0–0) *versus* 0 (0–1)) were worse at 2–5 years' follow-up than the 1-year scores ($P < 0{\cdot}05$ all values). Heartburn (0 (0–0) *versus* 0 (0–1)), dysphagia (0 (0–0) *versus* 1 (0–1)), DeMeester (0 (0–1) *versus* 1 (1–2)) and abdominal pain (0 (0–0) *versus* 1(0–1)) scores were worse at 5–8 years' follow-up compared with the 1-year scores ($P < 0{\cdot}05$ all values). Irrespective of this, heartburn, regurgitation and DeMeester scores remained significantly better at longer-term follow-up times than before operation ($P < 0{\cdot}001$). All other symptom scores (regurgitation, chest pain, epigastric pain, postprandial faintness, postprandial bloating, ability to burp, increased flatus and persistent diarrhoea) were not significantly different from 1-year scores at longer-term follow-up.

One hundred and nine patients (78 per cent) had postoperative 24-h pH tests, 95 per cent of which showed normal distal oesophageal acid exposure times (median acid exposure time 0·1 (range 0–46) per cent). In five patients (4 per cent) pH monitoring indicated recurrence of gastro-oesophageal reflux (total acid exposure time more than 4 per cent); one of these patients has had a redo fundoplication, and a second is awaiting reoperation. Symptoms in two others have been successfully controlled medically. The fifth is a patient with Barrett's oesophagus who is asymptomatic following surgery, despite a postoperative acid exposure time of 46 per cent. Nineteen patients (14 per cent) were taking antireflux medication at longer-term follow-up, eight for non-reflux symptoms. Seventeen of these 19 patients had a postoperative 24-h pH test, which was normal in 12.

Eleven patients (6 per cent) underwent reoperation, six for paraoesophageal herniation, four for obstructive symptoms and one for recurrent reflux. Nine of the 11 were reoperated on within 24 months of the initial operation. Seven were in the first 30 cases of the operative series.

Discussion

Antireflux surgery has an established place in the treatment of GORD. This is particularly true for patients whose symptoms are refractory to medical acid suppression therapy or who cannot take medication because of intolerable side-effects. In the past decade there has been a widening in the indications for fundoplication to include patients with medically controlled symptoms who prefer surgery to a lifetime of medication, and selected patients with reflux-related symptoms but with normal 24-h pH exposure times and no oesophagitis[10,12]. Introduction of the laparoscopic technique, with the twin appeals of a shorter hospital stay and a more rapid return to normal activities, has undoubtedly contributed to the expansion of antireflux surgery. Doubts have remained, however, about the long-term efficacy and durability of laparoscopic fundoplication[13, 14].

A number of long-term studies of open fundoplication have been published[13,15–25]. Care must be exercised when assessing and comparing such reports. Follow-up periods range from a mean of 4 years[25] to 20 years[19]. Some studies report consecutive series of patients operated on for GORD within a single institution[16,19–21,25], while others describe subgroups of patients selected according to the presence of erosive oesophagitis[18,23], Barrett's oesophagus[15,17] or for unstated reasons[24]. Follow-up rates range from 79 per cent[13] to 100 per cent[18]. Reported 'success' rates vary between 76 per cent in one 20-year follow-up study[19] and 91 per cent in an extrapolated actuarial analysis[25], although in the latter study only 35 of the original 100 patients were available for 5-year follow-up and three of the 100 for 10-years follow-up.

Reports of the long-term results of laparoscopic fundoplication are relatively few in number. The most complete report to date is that from Adelaide, which documents a 99 per cent follow-up rate on 178 patients at between 5 and 8 years after operation[26]. As with the current series, this included the learning curve experience, with the majority of the conversions (12 per cent overall *versus* 7 per cent in the present series) and reoperations (15 *versus* 6 per cent) occurring early on in the series. Irrespective of this, 87 per cent of patients were free from significant reflux symptoms at a median of 6 years following surgery and 90 per cent rated their outcome as 'good' or 'excellent'. Bammer *et al.*[27] reported on 171 of 291 patients who had undergone laparoscopic Nissen fundoplication at least 5 years previously; 93 per cent were satisfied with their decision to undergo surgery.

In the present study, 80 per cent of the surgical population supplied follow-up information at a mean of 48 months after surgery. Although data on the remaining 20 per cent may have altered the overall results, the follow-up rate of 80 per cent is comparable to that in most previous reports of open and laparoscopic fundoplication. The overall patient satisfaction rate of 91 per cent compares well with that of other laparoscopic reports, and matches the results of open surgery. The inclusion of patients from the learning curve experience with the laparoscopic technique partly explains the poorer outcome scores seen in the group who were assessed 5 years or more after operation. In particular, patients whose operation was converted from a laparoscopic to an open procedure fared less well; with their exclusion, the group 1 (2–5 years' follow-up) and group 2 (more than 5 years' follow-up) results converge. Minor changes in surgical technique during the series may have relevance to the observed outcome. The switch from silk to Ethibond® sutures was prompted by the reoperations for wrap herniation, during which no trace of the original silk suture material could be found. The addition of routine, as opposed to selective, crural repair has resulted in a marked reduction in the incidence of acute paraoesophageal hernia, with no appreciable effect on dysphagia scores or dilation rates. It must also be remembered that the advanced laparoscopic and optical equipment available nowadays bears little relation to the basic instrumentation and optical representation that were the norm a decade ago. It is likely that technical factors such as these, rather than a true deterioration in outcome 5 years or more following surgery, account for some of the differences in outcome seen between groups 1 and 2. A further indication of this is the fact that most patients with a poor modified Visick score at 5 years or more already had a poor score at 1 year.

Analysis of the paired data sets from 1 year and longer-term follow-up indicated a discernible worsening in symptoms of heartburn, dysphagia and abdominal pain, and in the DeMeester Symptom Score between the two follow-up periods. Although statistically significant, this observation is unlikely to be of clinical relevance for the vast majority of patients undergoing surgery, since the observed changes reflect, at worst, the occurrence of mild symptoms instead of no symptoms at all. Further assessment will ascertain if this trend continues with longer periods of follow-up of patients operated beyond the learning curve.

The varying responses in this study to the questions on outcome reflect the difficulty of assessing the results of surgery. For example, although 22 patients graded themselves as Visick III or IV, indicating a 'fair' or 'poor' result, 15 of these felt that surgery had improved their reflux symptoms and 11 believed that their operation had been a success. This may explain the discrepancy between the Visick I or II rate of 84 per cent and the patient satisfaction rate of 91 per cent. Clearly a significant number of patients who have symptoms or side-effects following surgery, or who still require regular medication, are still of the opinion that they are better off after fundoplication than they were beforehand.

It is worth noting that use of antireflux medication following antireflux surgery does not necessarily indicate a failure of the procedure adequately to control gastro-oesophageal reflux[28]. A significant proportion of the present patients who were taking medication after operation were using it to relieve non-reflux symptoms such as bloating and epigastric pain, and had normal acid exposure times and improved reflux symptoms. Patients who have been advised adequately before operation as to which of their symptoms are likely to be improved by surgery and which will remain unaffected are clearly more likely to have appropriate expectations of their eventual outcome. Improvements have been made in this advice with time. Regardless of this, the proportion taking antireflux medication after operation falls far short of the 62 per cent quoted in a recent report of the long-term results of a trial of medical treatment *versus* open Nissen fundoplication[13].

The learning curve phenomenon for laparoscopic antireflux surgery has been well documented[29]. To date long-term follow-up studies on laparoscopic fundoplication have included patients from the learning curve and as a result show misleadingly high rates for conversion and reoperation. The results from patients operated on beyond this initial learning curve experience can be expected to show further improvements in long-term outcome, thus demonstrating the efficacy and durability of laparoscopic fundoplication in the treatment of GORD. The results reported here, along with other recent reports of long-term outcome following laparoscopic fundoplication[26,27], give a fair reflection of what can be expected from antireflux surgery performed for appropriate indications by experienced laparoscopic surgeons.

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Diethylmaleate, a pro-oxidant, attenuates experimental ischaemia–reperfusion-induced lung injury

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Background: Systemic ischaemia–reperfusion (IR) injury is in part an oxidant injury mediated by neutrophils. Diethylmaleate (DEM), an intracellular pro-oxidant agent, has been shown to alleviate neutrophil-mediated tissue injury. The aim of this study was to evaluate whether DEM could have a protective effect on neutrophil-mediated lung injury in an animal model of lower-torso IR.

Methods: Sprague–Dawley rats (seven per group) were randomized into three groups. The control group underwent midline laparotomy only; the IR group underwent laparotomy and clamping of the infrarenal abdominal aorta for 30 min followed by 2 h of reperfusion; and the third group was pretreated with DEM 6 mmol/kg intraperitoneally 1 h before the IR insult.

Results: IR resulted in a significant increase in both microvascular leakage and pulmonary neutrophil infiltration as measured by bronchoalveolar lavage protein concentration and pulmonary myeloperoxidase activity respectively. Pretreatment with DEM significantly attenuated both microvascular leakage and neutrophil infiltration.

Conclusion: Preconditioning with DEM protected against IR-induced lung injury. This protective effect raises the possibility of using pro-oxidants to prevent inflammatory injury.

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Introduction

Ischaemia–reperfusion (IR) injury is a complex phenomenon often encountered in surgical practice. Typically, it is associated with both local injury and induction of the systemic inflammatory response[1]. Neutrophils are thought to play a key role in the pathogenesis[2–5]. Oxidants, proteases and elastases released by neutrophils have been implicated in the widespread endothelial damage and microvascular leakage[6,7]. Recent data have suggested that lung injury may be reduced by limiting cell activation. There is accumulating evidence that alterations in the cellular redox state play a critical role in cell signalling through modulation of tyrosine phosphorylation[8], regulation of transcription[9] and alterations in messenger RNA stability[10]. This suggests that administration of antioxidants or sulphydryl-reactive agents may have important modulatory effects on cell activation.

Glutathione, the most abundant intracellular thiol[11,12], has been shown to maintain the intracellular redox state[13]. However, diethylmaleate (DEM), a glutathione-depleting agent, has been shown paradoxically to protect against cellular injury in models of endotoxaemia[14,15].

The aim of this study was to determine whether pretreatment with DEM attenuates IR-induced acute lung injury in a rodent model of aortic cross-clamping and reperfusion.

Materials and methods

All animal procedures were carried out in an approved animal research facility, under licence from the Department of Health and Children, Republic of Ireland. Twenty-one adult male Sprague–Dawley rats weighing 300–400 g were anaesthetized with halothane (IIG, Dublin, Ireland). An external jugular venous catheter was inserted for heparin administration. Core temperature was monitored for the duration of the experiment using a rectal temperature probe (Hewlett–Packard, Boeblingen, Germany).

Aortic occlusion and reperfusion

Animals were randomized to one of three groups: control, IR, and IR with DEM pretreatment. All animals were fed standard rat chow before the experiment and given water to drink *ad libitum*. In the DEM-treated group, animals received DEM (Sigma Chemicals, Poole, UK) 6 mmol/kg by intraperitoneal injection 1 h before the experiment. This dose was based on previous work showing attenuation of lipopolysaccharide-induced lung injury after 6 mmol/kg intraperitoneally[16], and a review of previous regimens and their efficacy and side-effects in animal experiments[11,17]. Control animals received a similar volume of saline solution by means of intraperitoneal injection. Anaesthetized animals underwent a midline laparotomy. Following systemic heparinization (400 units/kg; Leo Laboratories, Dublin, Ireland), the infrarenal aorta was exposed. In control animals the aorta was exposed but not clamped. In the IR group and the DEM-treated group, the aorta was clamped using a microvascular clamp. This clamp was released after 30 min, enabling the lower limbs to be reperfused for a further 2 h. At the end of the experiment, the animals were killed with an overdose of anaesthetic. After sternotomy, the left main bronchus was clamped. Bronchoalveolar lavage of the right lung was performed with 2 ml normal saline containing ethylenediamine tetra-acetic acid 0·07 mol/l; this was repeated three times. The combined lavage returned (3–4 ml) was centrifuged at 1500 r.p.m. for 20 min at 4°C and subsequently assessed for protein concentration.

Myeloperoxidase assay

Neutrophil infiltration in lung was assessed by measuring myeloperoxidase (MPO) activity. MPO is a haem-containing enzyme within the azurophil granules of neutrophils. MPO was measured by a simple quantitative method of detecting leucosequestration. The right ventricle was cannulated using a 25-G needle (Jelco, Critikon, Basingstoke, UK) and the right pulmonary hilum was clamped. The pulmonary vasculature of the left lung was flushed using 50 ml saline to clear the lung of intravascular neutrophils. After weighing, the left lung was homogenized in 10 ml potassium phosphate buffer 50 mmol/l, pH 6, containing 0·5 per cent hexadecyltrimethyl ammonium bromide. The homogenate was freeze-thawed twice and centrifuged at 12 000*g* for 15 min. The resultant supernatant was assayed spectrophotometrically for MPO activity by incubating 0·1 ml of the supernatant with 2·9 ml of a solution containing 2·9 ml *O*-dioniside dihydrochloride in 90 ml distilled water, 5 ml 50 mmol/l potassium phosphate buffer (pH 6·0) and 5 ml 0·0006 per cent hydrogen peroxide. The change in absorbance with time at 460 nm was then recorded (CPU 8720, UV/VIS scanning spectrophotometer; Philips, Eindhoven, The Netherlands). One unit of MPO was defined as that degrading 1 mol peroxide per min at 25°C.

Bronchoalveolar lavage

Lung lavage fluid protein content was measured spectrophotometrically using the Lowry method[18]. Neutrophil counts in bronchoalveolar lavage fluid were carried out by Diff–Quick staining and consecutive counting of neutrophils per high-power field.

Statistical analysis

Results are expressed as mean(s.e.m.). Statistical analysis was carried out using analysis of variance for comparison of multiple means with *post hoc* Scheffe test analysis. Significance was accepted for $P < 0{\cdot}05$.

Results

Effect of ischaemia–reperfusion on pulmonary neutrophil infiltration

Ischaemia followed by reperfusion resulted in a significant increase in pulmonary neutrophil infiltration, as indicated by an increase in MPO activity from 144·22(9·85) units/g in control animals to 210·40(10·56) units/g in the IR group ($P < 0{\cdot}01$). This increase was significantly attenuated by pretreatment with DEM to 161·79(5·62) units/g ($P < 0{\cdot}01$).

IR resulted in significantly higher levels of bronchoalveolar lavage neutrophil concentration (928·25(57·17) per mm^3) compared with values in controls (134·60(18·34) per mm^3) ($P < 0{\cdot}01$). Pretreatment with DEM significantly reduced neutrophil concentration in bronchoalveolar lavage fluid (284·44(42·75) per mm^3; $P < 0{\cdot}01$ *versus* IR group).

Effect of ischaemia–reperfusion on pulmonary microvascular permeability

Pulmonary microvascular permeability after IR, as assessed by protein concentration, was significantly increased in untreated animals compared with control and DEM-pretreated groups. Protein concentration in the IR group was 585·26(96·00) µg/ml *versus* 191·15(22·82) µg/ml in the control group ($P < 0.01$). In the DEM group, the rise in protein concentration seen in the untreated group following reperfusion was significantly decreased to 288·87(47·53) μg/ml ($P < 0.02$ *versus* IR).

Discussion

The hypothesis was that pretreatment with DEM might attenuate lung injury secondary to lower-torso IR. This study confirmed that temporary clamping of the infrarenal aorta resulted in altered pulmonary endothelial barrier function, with increased protein concentration and neutrophil infiltration. However, preadministration of the glutathione-depleting agent DEM significantly decreased the lung injury.

The role of the neutrophil in initiation and promotion of oxidative damage in the lung following lower-torso reperfusion injury is well established[2–5]. The authors and others have previously demonstrated this phenomenon in an animal model of lower-limb ischaemia and revascularization[19,20]. Inflammatory stimuli, such as the proinflammatory cytokines and chemokines tumour necrosis factor α, interleukin (IL) 1 and IL-8, are thought to initiate a cascade of events that leads to the expression of adhesion molecules on the endothelial cells and, ultimately, neutrophil activation and sequestration[21]. This is mediated by the interaction between the CD11b–CD18 adhesion glycoprotein complex on the neutrophil and its complementary ligand (intercellular adhesion molecule (ICAM) 1) on the endothelial cell. Neutrophil activation is regarded as one of the key mediators of distant organ damage and dysfunction[2,22]. After adhering to pulmonary microvascular endothelium, neutrophils exert their toxic effects through the release of proteolytic enzymes and free radicals[22,23].

Numerous therapeutic modalities have been proposed to counteract this injury, including antioxidants[24], leucocyte depletion[25], thermotolerance[26], antiproteolytic agents and monoclonal antibodies to specific neutrophil adhesion receptors[4,27]. Recent studies, however, have suggested that greater success at attenuating lung injury may be achieved by manipulating the intracellular redox state of the cell, and hence cell activation. Glutathione maintains this intracellular redox state by the detoxification of oxidized moieties by the activity of glutathione peroxidase, glutathione *S*-transferase and a direct oxidant scavenging effect[13]. This study demonstrated that the administration of DEM, a glutathione-depleting agent, paradoxically attenuated the oxidant-mediated lung injury. Several other studies have also demonstrated paradoxical beneficial effects associated with glutathione depletion, including a reduction in hepatic injury following systemic endotoxaemia[15] and an improvement in survival after cerebral IR[14].

The mechanism by which DEM induced these changes is not clear. O'Neill *et al.*[28] showed that DEM induced neutrophil apoptosis, via the caspase 3 pathway. Nathens *et al.*[17] demonstrated that DEM reduced neutrophil sequestration by decreasing endotoxin-induced ICAM-1 expression on the surface of pulmonary endothelium. DEM has also been reported to reduce core body temperature by approximately 3·0°C[29], but this hypothermic effect is an unlikely explanation for the present findings because core temperature was maintained throughout the experiment by using warming blankets, and monitored with a rectal probe.

A DEM-only group was not included in this study. This might have been useful in determining whether DEM itself can lead to injury. However, previous studies have shown no significant difference in injury between animals treated with DEM and controls[16]. The delay between administration of DEM and the IR injury was based on previous studies demonstrating that 1 h was optimal. Investigations are currently under way to establish whether DEM is also active after the insult.

Manipulation of the cellular redox state by use of the glutathione-depleting agent DEM may prove useful in modulating the broad range of diseases characterized by neutrophil infiltration. While lowering the predominant endogenous cellular antioxidant may appear an unlikely therapy, this strategy may succeed on account of prevention of the neutrophil influx associated with IR injury.

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The authors acknowledge the expert assistance of D. Borwick and M. Dunphy of the Department of Surgery, Beaumont Hospital, Dublin. This work was supported by a research grant from the Royal College of Surgeons in Ireland.

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Original article

Risk of femoral hernia after inguinal herniorrhaphy

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Background: Small case series have suggested an increased risk of femoral hernia after previous inguinal herniorrhaphy, but no large-scale data with complete follow-up are available.

Methods: Data were extracted from the Danish Hernia Database covering the interval from 1 January 1998 to 1 July 2001, and included 34 849 groin hernia repairs.

Results: Of 1297 femoral hernia repairs, 71 patients had previously had an operation for inguinal hernia within the observation period. These 71 femoral hernias represented 7·9 per cent of all reoperations for groin hernia recorded in the database. The median time to reoperation for a 'recurrent' femoral hernia after previous inguinal herniorrhaphy was 7 months, compared with 10 months for inguinal recurrences. The risk of developing a 'recurrent' femoral hernia after previous inguinal herniorrhaphy was 15 times higher than the rate of femoral hernia repair in the general population.

Conclusion: This study of 34 849 groin hernia repairs demonstrated a 15-fold greater incidence of femoral hernia after inguinal herniorrhaphy compared with the spontaneous incidence. These femoral recurrences occurred earlier than inguinal recurrences, suggesting that they were possibly femoral hernias overlooked at the primary operation.

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Introduction

It is well established that femoral hernia comprises only about 3–4 per cent of all groin hernia repairs[1–3]. Several case series have suggested an increased risk of femoral hernia after previous inguinal herniorrhaphy[1,4–9]. The question remains, however, whether a femoral hernia after previous inguinal herniorrhaphy represents an overlooked femoral hernia or a new 'spontaneously' developed femoral hernia. These questions cannot be answered from the literature because of the small size and insufficient follow-up of published series.

The establishment of large national or regional databases monitoring all groin hernia surgery[3,10] provides unique possibilities for describing the incidence and exact time course for the development of a femoral hernia after a previous inguinal herniorrhaphy. The aim of this study was, therefore, to describe the incidence and time course of operation for femoral hernia after previous inguinal herniorrhaphy, based on the Danish Hernia Database, which included 34 849 patients from January 1998 to July 2001.

Patients and methods

Data were extracted from the Danish Hernia Database, which started registration on 1 January 1998[3]. The database collaboration includes approximately 10 000 groin hernia repairs per year, presently representing more than 98 per cent of all groin herniorrhaphies performed in Denmark.

The following information was extracted from the database: (1) the number of femoral hernia repairs in patients never operated on before for a groin hernia and (2) the number of femoral hernia repairs performed in patients who previously had an operation for inguinal or femoral hernia but after 1 January 1998. Thus, femoral hernias that occurred after a previous groin hernia repair performed before 1 January 1998 were not included, because specific information on the first hernia repair could not be obtained. A total of 107 combined femoral and inguinal herniorrhaphies was excluded from the analysis.

Results

Between 1 January 1998 and 1 July 2001, 34 849 groin hernia repairs were recorded in the Danish Hernia

Table 1 Distribution of age and sex in 71 patients who had femoral hernia repair after a previous inguinal herniorrhaphy

	Men	Women
Age (years)		
< 40	7	5
40–60	8	15
> 60	29	7
Total	44	27

Table 2 Type of previous inguinal herniorrhaphy in 71 patients who had subsequent reoperation for a femoral hernia and the distribution of repairs for inguinal hernia in the total population in the Danish Hernia Database (*n* = 33 552)

	Femoral 'recurrence' (*n* = 71)	Inguinal operations in database (*n* = 33 445)
Sutured posterior wall repair (except McVay)	20 (28·2)	7 960 (23·8)
McVay	1 (1·4)	739 (2·2)
Lichtenstein repair	38 (53·5)	17 971 (53·7)
Other mesh (plug, etc.)	10 (14·1)	5 146 (15·4)
Laparoscopic	2 (2·8)	1 629 (4·9)

Values in parentheses are percentages

Database. Of these, a femoral hernia repair was performed in 1297 patients (3·7 per cent).

Among the 1297 femoral herniorrhaphies, 71 patients previously had an inguinal hernia repair within the observation interval, representing 5·5 per cent of all femoral hernia repairs. Nine (12·7 per cent) of the 71 patients had an acute operation for the femoral hernia.

The 71 femoral hernias after previous inguinal herniorrhaphy represented 7·9 per cent of all reoperations for groin hernias recorded in the database (898 operations).

The distribution of age and sex among the 71 patients with a 'recurrent' femoral hernia after previous inguinal herniorrhaphy is shown in *Table 1*. Although more hernias occurred in older patients, the age distribution did not allow useful separation into high-risk groups. The distribution of the various types of inguinal herniorrhaphy in patients with a subsequent femoral hernia (*n* = 71) and the distribution of all inguinal hernia repairs recorded in the Danish Hernia Database (*n* = 33 445) are shown in *Table 2*. The distribution of the different types of groin hernia repair was similar between patients with a femoral 'recurrence' after previous inguinal herniorrhaphy and all patients in the Danish Hernia Database who had an inguinal hernia repair. Among the 71 femoral recurrences, 23 patients (32·4 per cent) had had a previous recurrent inguinal hernia repair.

The time course of femoral hernia repair in relation to the previous inguinal hernia repair is shown in *Fig. 1*, together with the time course of reoperation for an inguinal hernia after previous inguinal herniorrhaphy. The median time to reoperation of the femoral 'recurrence' was 7 months, whereas the median time to reoperation for an inguinal recurrence was 10 months.

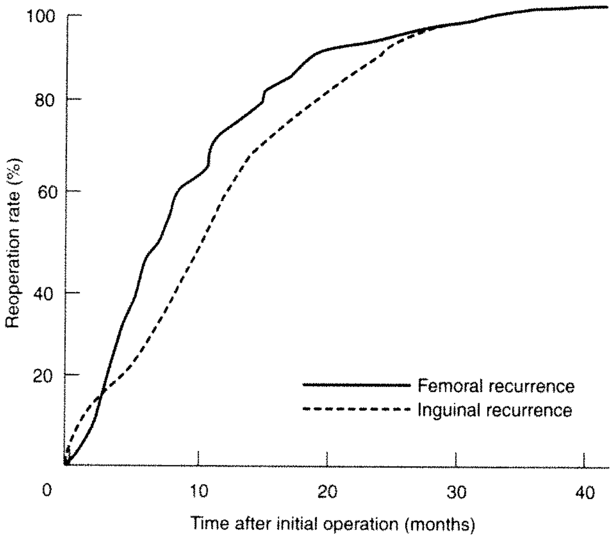

Fig. 1 Time course for reoperation for a 'recurrent' femoral or inguinal hernia after previous repair of an inguinal hernia

The number of 'recurrent' femoral hernias that occurred after inguinal herniorrhaphy was 71. The expected number of spontaneous femoral hernias occurring among 33 445 normal subjects aged over 18 years was 4·9 (calculated from the observed 1226 femoral operations in 4·2 million inhabitants aged over 18 years during 3·5 years). Therefore, these data suggest that the risk of a 'recurrent' femoral hernia after previous inguinal herniorrhaphy is about 15 times higher than the rate of femoral hernia repair.

Discussion

The main finding of this study was a 15-fold higher incidence of femoral hernia repair in patients who had previously had an inguinal hernia repair compared with the spontaneous operation rate for a femoral hernia. Furthermore, the 'recurrence' of a femoral hernia after a previous inguinal herniorrhaphy was observed earlier than an inguinal hernia recurrence (7 *versus* 10 months).

These findings are in accordance with several previous observational studies that reported early recurrence of a femoral hernia after previous inguinal herniorrhaphy[1,4–9]. However, the small size of these case series and the lack of large-scale prospective studies with complete follow-up have not enabled quantification of the risk of a femoral hernia recurrence after previous inguinal herniorrhaphy. In the present study, the follow-up rate was over 98 per cent[3].

Femoral hernias usually occur in elderly women, but the femoral hernias that developed after previous inguinal herniorrhaphy in the present study appeared mainly in men and with a mean age of over 60 years (*Table 1*). However, the distribution in age and sex groups did not allow separation into clinically useful high-risk groups.

The pathogenesis of the increased incidence of femoral hernia after a previous inguinal herniorrhaphy is unknown, but previous studies have suggested that they may represent an overlooked hernia or a new 'spontaneous' femoral hernia due to widening of the femoral canal by the inguinal herniorrhaphy[4]. However, the type of inguinal hernia repair did not seem to be important, because the distribution of type of initial operation in the patients who developed a femoral hernia was similar to that in the background population of all patients undergoing inguinal herniorrhaphy (*Table 2*). The use of a Lichtenstein tension-free repair might cause less traction and widening of the femoral canal, but apparently did not reduce the risk of developing a femoral hernia. However, 23 (32·4 per cent) of the 71 'recurrent' femoral hernias developed in patients who had previously had repair of a recurrent inguinal hernia, suggesting that these patients might be at increased risk; recurrent inguinal hernias comprised only 14·9 per cent (4998 of the 33 445 patients having operation for an inguinal hernia).

Early reoperation for a femoral hernia after previous inguinal herniorrhaphy suggests that these hernias represent hernias overlooked at the first inguinal hernia repair. These findings may, therefore, support the recommendation to explore the femoral canal routinely during inguinal herniorrhaphy[1,4,8,11–14]. However, there are no prospective comparative data to show whether this might decrease the risk of developing a subsequent femoral hernia. The feasibility of exploration of the femoral canal during operation under local anaesthesia is not known. Finally, it is not clear whether femoral hernia can be diagnosed by palpation during groin hernia repair, or whether the palpation of a minor protrusion will lead to unnecessary surgery. The extent to which Danish surgeons routinely explore the femoral canal during inguinal herniorrhaphy remains unknown, but in only 107 of 34 849 operations was a combined femoral–inguinal hernia diagnosed and repaired at the operation.

Acknowledgements

This work was supported by a grant from Helsefonden, the Danish Institute for Health Technology Assessment, the H:S Copenhagen Hospital Corporation, the Danish Research Council (9902757) and the Danish Health Ministry.

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Correspondence

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Intragastric balloon in the treatment of patients with morbid obesity (*Br J Surg* 2001; 88: 1245–8)

Sir

The authors' arguments hinge on the statement 'a reduction in BMI is desirable before embarking on definitive antiobesity procedures to reduce operative risk…'. This is not supported by any data or reference. The paper by Weiner *et al.*[1] had no control group and De Waele *et al.*[2] described two patients only. In the presented series, there was a 5 per cent risk of laparotomy for major complications associated with the balloon. The conversion rate for gastric banding is 1·4 per cent with a major postoperative morbidity rate of 0·57 per cent[3]. Furthermore, this morbidity is unrelated to body mass index (BMI). It is hard to agree with the authors that this procedure is either necessary, cost effective (as it costs around £300) or safe. Intragastric balloon placement should not be used because of inexperience in other techniques.

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Gender differences in long-term survival of patients with colorectal cancer (*Br J Surg* 2001; 88: 1092–8)

Letter 1

Sir

If the survival difference between men and women is due to a better immune response in women, the role of sex steroids or other gender-related factors, this implies a difference in the biology of rectal and colonic cancers, for which there is not much evidence. Because the survival advantage is only in rectal cancer, could there be an influence of pelvic anatomy and the potential for more radical resection in women? I wonder whether the authors could tell us whether there was a difference in the local recurrence rates after surgery for rectal cancer between men and women?

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Letter 2

Sir

An additional explanation may be found within the insulin-like growth factor (IGF) system. The IGFs are multifunctional regulatory peptides with characteristics of both classical 'endocrine' hormones and tissue growth factors. IGF-I is both mitogenic and antiapoptotic, while its main binding protein, IGFBP-3, is pro-apoptotic. There is considerable interindividual variation in circulating levels of IGF-I and IGFBP-3, and this heterogeneity in IGF physiology may determine cancer risk. Recent epidemiological studies have shown that circulating IGF-I is positively, and IGFBP-3 inversely, associated with the development of many common malignancies, including colorectal cancer[1]. Two studies of colorectal adenomas have shown that these associations are restricted to advanced polyps, suggesting that an individual's IGF-I/IGFBP-3 profile may influence adenoma progression[2,3]. By extrapolation, the IGF-I/IGFBP-3 profile may influence colorectal cancer progression, and ultimately survival.

With regard to gender differences, there are no differences between mean serum IGF-I levels in adults aged under 50 years, but thereafter mean values are higher in men[4]. By contrast, mean serum IGFBP-3 levels are lower in males over 50 years old, such that the IGF-I/IGFBP-3 ratios for men and women progressively diverge after the menopause (*Fig. 1a*). This pattern mirrors the gender differences for colorectal cancer incidences in the general population (*Fig. 1b*)[5]. These factors may also influence survival.

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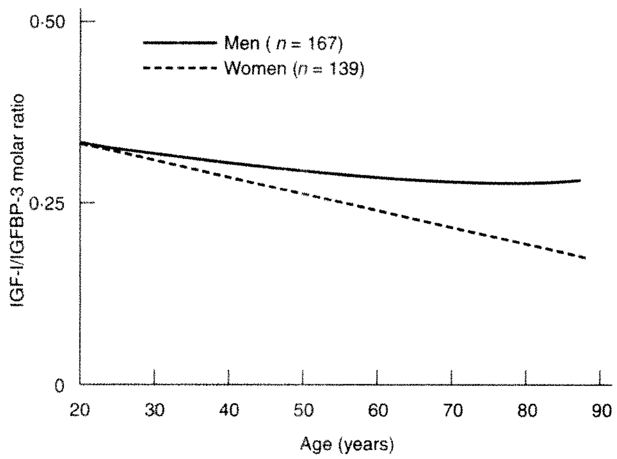
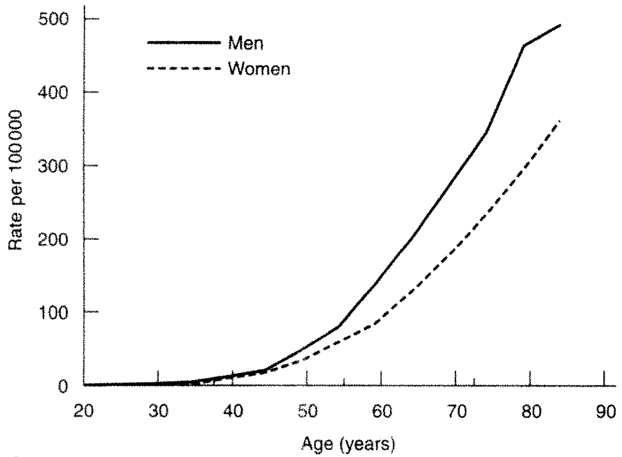


a IGF-I/IGFBP-3 molar ratios



b Incidence of colorectal cancer

Fig. 1 **a** Mean insulin-like growth factor (IGF) I/IGF binding protein (BP) 3 molar ratios for men and women aged 20–90 years. Data generated from a healthy population (n = 306) using IGF-I and IGFBP-3 assays[4]. For molar conversions, 1 µg/l is 0·130 nmol/l for IGF-I and 0·036 nmol/l for IGFBP-3. **b** Age-specific standardized incidence of colorectal cancer in men and women in England and Wales[5]

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Letter 3

Sir

This carefully designed and well executed study demonstrates a 'significant gender difference' in disease-free and overall survival following curative resection for rectal carcinoma. While treatment bias by sex was not found, possible treatment bias by age was potentially unaccounted for.

At present, the optimal therapeutic regimen for patients with Union Internacional Contra la Cancrum (UICC) stage II and III disease is surgery plus chemoradiotherapy[1]. However, the rates for patients undergoing this treatment decline dramatically with increasing age[2], even after adjusting for demographic and clinical characteristics and after exclusion of patients with any evident co-morbidity. These results were confirmed by our own study[3]; younger patients (less than 75 years or more) were significantly more likely to have undergone a surgery-based multimodality regimen than elderly patients (those aged 75 years or more). Furthermore, among UICC II and III elderly patients, there was a significant survival advantage for those receiving surgery plus adjuvant therapy compared with those who received surgery only (P = 0·001). In this context, it is noteworthy that the majority of the cohort in Wichmann's study presented with UICC II and III carcinoma and that mean age at primary resection for women was significantly older than in men. A selection bias may be present in this subsample, confounding an even more pronounced result. With an ageing population and better chemotherapeutic support, denying patients potentially valuable therapy based on age may no longer be acceptable.

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Late mortality in patients with severe acute pancreatitis (*Br J Surg* 2001; 88: 975–9)

Sir

These results are in marked contrast to those reported from Scotland where the mortality rate from acute pancreatitis (all attacks) was 7·5 per cent, and 53·7 per cent of all deaths occurred in the first week[1]. It is likely, however, that the patients with the most severe attacks die before transfer to specialist centres or that elderly patients, who are at the highest risk of death, may be considered unsuitable for intensive therapy and transfer. A fatal outcome may be better predicted using the Multiple Organ Failure (MOF) score rather than the Acute Physiology And Chronic Health Evaluation II scoring system[2]. Could the authors please comment on the proportion of their patients who were transferred from other hospitals and present the MOF scores at the time of admission to hospital?

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Authors' reply

Sir

Our results are indeed in marked contrast to those reported by many others as already indicated in the manuscript (references 14–21). Of the 106 patients 39 (40 per cent) were transferred from other hospitals. In the group of ten patients who died from acute pancreatitis, six were transferred from other hospitals. It is possible that patients with a severe attack may die before they are transferred to the specialist centre but in Switzerland it is rare for a clinician in an outside hospital to be unable to access an intensive care bed. The documented Acute Physiology And Chronic Health Evaluation II score during the first week of the disease and the number of patients transferred indicate that severely ill patients were indeed sent to the university hospital. The median age of patients who died was 61·5 (range 32–73) years, and 57 (range 28–87) years for those who survived.

The aggressive early severity staging and initiation of intensive care treatment are the cause of the low early mortality rate rather than the fact that a patient with severe disease may not have been sent to our centre.

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Randomized double-blind controlled trial of roxithromycin for prevention of abdominal aortic aneurysm expansion (*Br J Surg* 2001; 88: 1066–72)

Letter 1

Sir

The rationale for antibiotics cited was the possibility of infection within the aneurysm by *Chlamydia pneumoniae*. The association between *C. pneumoniae* and arterial disease is well recognized, but there is no proof that *C. pneumoniae* plays any clinically significant role[1]. It is currently not known whether live organisms are needed to mediate damage, or whether persistent chlamydial antigens from phagocytosed bacteria could promote inflammation, and the authors acknowledge that macrolide antibiotics also have significant anti-inflammatory properties. This study cannot discriminate between subjects with or without aneurysmal *C. pneumoniae* as raised antichlamydial antibody titres do not predict the endovascular presence of the organism. The apparent slowing of aneurysm expansion could be due to a true antibiotic effect of roxithromycin or the consequence of another property of the drug. The authors suggest that larger intervention studies are required to confirm their results. Large multicentre antibiotic intervention trials are ongoing[2] but even if they report better outcomes for patients randomized to antibiotics the mechanism of action will not have been elicited.

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1 Gibbs RG, Sian M, Mitchell AW, Greenhalgh RM, Davies AH, Carey N. *Chlamydia pneumoniae* does not influence atherosclerotic plaque behaviour in patients with established carotid artery stenosis. *Stroke* 2000; 31: 2930–5.

2 Dunne M. WIZARD and the design of trials for secondary

prevention of atherosclerosis with antibiotics. *Am Heart J* 1999; **138:** S542–4.

Letter 2

Sir

These results must be interpreted with some caution; the differences in aortic diameter are small and well within the accepted range for intraobserver error. The authors have calculated their intraobserver variation, but do not tell us what this is.

The aetiology of abdominal aortic aneurysms (AAAs) is not understood but the role of metalloproteinases, in particular the gelatinases matrix metalloproteinase (MMP) 2 and MMP-9, has been well established in recent years and by the authors themselves. As a result a number of studies have focused on the MMP inhibitory properties of the tetracycline group of antibiotics and demonstrated encouraging results in both organ culture[1] and animal models[2] of aneurysmal disease. These studies have led to a proposed prospective randomized clinical trial in the USA using two doses of doxycycline *versus* placebo. Initial power calculations suggest the need for 350 patients and 4 years of follow-up to detect a significant difference[3]. These studies challenge the authors' hypothesis that treatment of chlamydial infection reduces AAA expansion rate. The evidence to date suggests that the MMP inhibitory properties of tetracyclines prevent matrix degradation within the aortic wall and that this is independent of their antimicrobial activity.

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Authors' reply

Sir

Chronic inflammation may be a contributing factor in the pathogenesis of abdominal aortic aneurysms (AAAs). *Chlamydia pneumoniae* may be the trigger of the chronic inflammation and subsequently the formation and expansion of AAA.

Elastolytic matrix metalloproteinases (MMPs) are involved in the development of AAAs[1] and *C. pneumoniae* induces the production of MMPs by macrophage activation[2]. In an animal model it was shown that *C. pneumoniae* induced both macrophage influx and aneurysm formation[3]. It is therefore a possibility that *C. pneumoniae* exerts its effect on AAAs through MMPs. MMPs and *C. pneumoniae* do not necessarily represent two independent aetiologies as suggested by Boyle.

The observed effect found in our study may therefore be due to the anti-inflammatory activity of roxithromycin rather than its antichlamydial activity. A clarification of this would require testing a drug with the same anti-inflammatory effects and no antichlamydial effects.

The aim of our study was to investigate the effect of roxithromycin on AAA expansion rates. We agree that our study does not prove the clinical role of *C. pneumoniae*, but this was not the intention. It was a reasonable part of the rationale behind the study.

If the beneficial findings of roxithromycin on AAAs is confirmed in larger studies it should be considered a treatment, regardless of mechanism of action, especially if the effects outweigh the ecological concerns of spread of resistance in the community. Because of this concern we feel it is important to assess tetracyclines and macrolides with anti-inflammatory activity and with no antimicrobial activity, whenever such drugs may arise.

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1 Pyo R, Lee JK, Shipley JM, Curci JA, Mao D, Ziporin SJ *et al.* Targeted gene disruption of matrix metalloproteinase-9 (gelatinase B) suppresses development of experimental abdominal aortic aneurysms. *J Clin Invest* 2000; **105:** 1641–9.
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Effect of *Helicobacter pylori* eradication on the ulcer recurrence rate after simple closure of perforated duodenal ulcer: retrospective and prospective randomized controlled studies (*Br J Surg* 2001; 88: 1054–8)

Letter 1

Sir

The relationship between *Helicobacter pylori* infection and perforated duodenal ulcer may not be as significant as in patients with uncomplicated duodenal ulcer disease, primarily due to a lower *H. pylori* infection rate in patients with perforated ulcer[1]. When the authors conclude that *H. pylori* eradication reduces ulcer recurrence rate, this could be conceived as a recommendation to give anti-*H. pylori* treatment to all patients with perforated ulcers irrespective of *H. pylori* infection status. Although randomized, the study may have flaws in design and presentation of data. (1) What was the reason for randomizing *H. pylori*-negative patients to anti-*H. pylori* treatment? (2) According to *Table 3* initial ulcer healing was achieved in 122 of 162 patients; did *H. pylori* status or the randomized treatments influence the ulcer healing rate 8 weeks after simple closure? (3) When presenting data on ulcer recurrence, what was the rationale for not using life-table methods? (4) Why did the authors not present the recurrence rates in relation to the two randomized anti-*H. pylori* treatments? The authors state that *H. pylori*-negative status is a useful predictor of non-recurrence. If as many as 40–50 per cent of the patients are *H. pylori*-negative at perforation, this will have a clinical impact on the postoperative management of patients, reserving anti-*H. pylori* treatment for *H. pylori*-positive patients only.

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1 Reinbach DH, Cruickshank G, McColl KEL. Acute perforated duodenal ulcer is not associated with *Helicobacter pylori* infection. *Gut* 1993, 34: 1344–7.

Letter 2

Sir

While it is may be concluded that in this population relapse following simple closure is significantly related to *H. pylori* infection, the paper does not support the final conclusion that eradication therapy can 'be recommended in all patients with a perforated duodenal ulcer and *H pylori* infection'. In the West, eradication rates of over 90 per cent can be achieved with short-course triple therapy. In this study, however, there was no significant difference in *H. pylori* eradication rates in the ranitidine and quadruple therapy groups beyond 8 weeks. Treatment failure is a common problem in the developing world and, as the authors point out, is thought to be due to metronidazole resistance. Reinfection by close family members has also been implicated[1]. In an Indian population it may be concluded that treatment of *H. pylori* will make no difference to the long-term outcome of patients presenting with duodenal ulceration and *H. pylori* infection. Side-effects of treatment and cost may outweigh any potential benefit. A study of definitive surgery *versus* simple closure and long-term drug therapy would be more relevant to the majority of the world's population.

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Authors' reply

Sir

Helicobacter pylori does not cause duodenal ulcer perforation, but eradication of the organism in patients who are positive after perforation closure reduces ulcer recurrence rate. *Table 3* shows a significant association between a positive *H. pylori* infection and recurrence or persistence at follow-up. Eradication is not indicated in patients without infection. Patients were randomized immediately after perforation closure since final *H. pylori* status was available only after serology at 8 weeks to allow for those recently infected. The aim of the study was not to assess eradication rates with different regimens. A standard regimen was chosen initially and subsequently continued without change because the study extended over several years. We now use omeprazole, clarithromycin and amoxycillin, and have an eradication rate of over 90 per cent[1]. Resistance in developing countries is primarily to nitroimidazoles[2]. Regimens without nitroimidazoles yield eradication rates comparable to those in the West. One cannot conclude, therefore, that eradication is futile in the long-term outcome of patients with duodenal ulcer perforation and *H pylori* infection in developing countries.

We have shown previously that only 42·2 per cent of patients have ulcer recurrence after simple closure[3] and that at the time of closure there are no reliable criteria for separating ulcers that are likely to recur from those that will remain healed[4]. Hence, definitive surgery as a uniform policy would be unnecessary in the majority of patients, besides carrying a potential for troublesome complications in other patients.

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Effects of adenosine on ischaemia–reperfusion injury associated with rat pancreas transplantation (*Br J Surg* 2001; 88: 1366–75)

Sir

This paper suffers from several important limitations by failing to address the potential effects of adenosine degradation products in the preservation solution. Adenosine has a short half-life (10 s) due to its rapid degradation by tissue adenosine deaminase[1]. Inosine, an adenosine degradation product, is biologically active[2], more metabolically stable than adenosine[3] and selectively binds to and stimulates the adenosine A_3 receptor[4], mediating its biological effects[5]. This study did not employ an adenosine deaminase inhibitor to prevent adenosine degradation. The findings cannot be unequivocally attributed to adenosine and may be due to inosine. Finally, theophylline, the adenosine antagonist used in this study, has other effects independent of adenosine receptor antagonism which probably account for most of its pharmacological actions[6]. These adenosine receptor-independent effects, such as phosphodiesterase inhibition, may have also influenced the observed results.

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Author's reply

Sir

The aim of our study was to determine whether the uptake of adenosine by tissue preserved in University of Wisconsin (UW) solution could modify the inflammatory response of the transplanted pancreas. The study concluded only that the adenosine present in the preservation solution can stimulate this response but it did not specify whether such an effect was mediated by inosine, xanthine or any of the other metabolites resulting from the organ biotransformation of the exogenous adenosine in the UW solution.

When we compare two identical UW solutions differing only in the presence or not of adenosine and we can detect differences between them in their end result, such an observation obviously indicates that the effects could be attributed only to the presence or lack of exogenous adenosine. Whether adenosine achieves its effects directly or through any of its metabolites was not the object of the study. This could be of interest for future studies.

Furthermore, the fact that the levels of adenosine metabolites are modified in the pancreas, consequent to adenosine uptake from the preservation solution, indicates again that any of them could be responsible for the observed effects. We did use theophylline, a well known specific adenosine receptor blocker, to discriminate for this possibility and although, as happens with many other experimentally used compounds, it could have some unspecific effects, it is also true that it has been used successfully in numerous studies on adenosine.

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Prospective analysis of quality of life and survival following mesorectal excision for rectal cancer (*Br J Surg* 2001; 88: 1617–22)

Sir

Quality of life impairment in patients with advanced colorectal cancer, particularly depression, correlates significantly with T lymphocyte activation as defined by increased serum levels of interleukin 2 soluble receptor α[1]. In addition, increased serum interleukin 2 soluble receptor α also predicts weight loss in such patients that is detrimental to survival[2]. The precise mechanism for the association between depression and interleukin 2 soluble receptor α is not clear. Tumour-initiated circulating products of immunological activation may cause depression by depleting serum tryptophan concentration, which results in the reduction of the neurotransmitter serotonin in the central nervous system[3]. We agree with the authors' conclusion that quality of life measurements should be performed in this setting and suggest that there is biochemical evidence for the use of selective serotonin reuptake inhibitors in patients with impairment of quality of life, particularly depression.

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1 Allen-Mersh TG, Glover C, Fordy C, Henderson DC, Davies M. Relation between depression and circulating immune products in patients with advanced colorectal cancer. *J R Soc Med* 1998; 91: 408–13.
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Stoma-related complications are more frequent after transverse colostomy than loop ileostomy: a prospective randomized clinical trial (*Br J Surg* 2001; 88: 360–3)

Sir

We are concerned about the incomplete description of the randomized controlled trial (RCT) reported in this paper. A checklist for such reporting is available[1] and was revised last year[2,3]. Edwards *et al.* have not detailed the randomization process (in particular sequence generation and allocation concealment), how the sample size was obtained and do not clearly define outcome measures. The χ^2 test with Yates' correction is unreliable for such small numbers.

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1 Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I *et al.* Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996; 276: 637–9.
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The authors of this article chose not to reply to the above letter.

Effect of multimodality therapy on circulating vascular endothelial growth factor levels in patients with oesophageal cancer (*Br J Surg* 2001; 88: 1105–9)

Sir

We agree that vascular endothelial growth factor (VEGF) detected in serum may not be derived solely from tumour cells and agree that macrophages could be an additional source. The authors do not discuss another recognized source, the platelet. The megakaryocyte constitutively produces VEGF[1] and platelets release it when activated *ex vivo* in the formation of serum[2]. This has obvious consequences for use of serum VEGF as a marker of tumour angiogenesis and it has been hypothesized that measurement of VEGF in plasma might be more appropriate[2]. The fact that serum VEGF levels did not fall following neoadjuvant chemoradiotherapy despite a favourable pathological response and the lack of correlation demonstrated with tumour stage tend to support the hypothesis that serum VEGF may not be a useful surrogate marker of the angiogenic status of the primary tumour. Alteration in serum VEGF levels may be influenced more by changes in platelet number than by tumour effects, and measurement of plasma VEGF should be more specific.

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1 Mohle R, Green D, Moore MA, Nachman RL, Rafii S. Constitutive production and thrombin-induced release of vascular endothelial growth factor by human megakaryocytes and platelets. *Proc Natl Acad Sci U S A* 1997; **94:** 663–8.

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Authors' reply

Sir

We readily acknowledge the role of the platelet as a source of vascular endothelial growth factor (VEGF)[1]. In our series controls and patients with cancer had serum prepared in a similar manner and there can be no doubt that, regardless of source, circulating VEGF levels are raised in patients with oesophageal cancer.

The majority of patients who die from oesophageal cancer do so as a result of local recurrence or distant metastases. It seems, therefore, that the important issue is not the angiogenic status of the primary tumour but rather the ability of residual occult deposits to develop following resection. Over 80 per cent of patients undergoing apparently 'curative' surgery for gastro-oesophageal cancer have rib bone marrow micrometastases[2]. If these cells are exposed to a potently pro-angiogenic fluid, their capability to develop into detectable disease is greatly enhanced.

We do not dispute that generating plasma can induce platelet activation with consequent VEGF release[3], but platelets are often activated in the tumour vasculature of patients with cancer[4]. An assessment of the total amount of VEGF present in the circulation, while not necessarily a direct reflection of tumour angiogenesis, may be a more appropriate measure of the potential for residual micrometastases to develop into clinically significant recurrent or metastatic disease.

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1 Verheul HM, Hoekman K, Luykx-de Bakker S, Eekman CA, Folman CC, Broxterman HJ *et al.* Platelet: transporter of vascular endothelial growth factor. *Clin Cancer Res* 1997; **3:** 2187–90.

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Estimating the benefits of adjuvant systemic therapy for women with early breast cancer (*Br J Surg* 2001; 88: 1513–18)

Sir

The authors have clearly pointed out that 70–95 per cent of women with node-negative disease are disease-free 10 years after local therapy. It is a dilemma, therefore, whether to subject a woman to the toxicities of systemic therapy if she has an up to 95 per cent chance of survival at 10 years. Surely it is even more of a dilemma if the woman is 40 as opposed to 74 years old?

It came to our attention that the 10-year cause-specific survival statistics analysed for all women aged 40–74 years (range 99·2–76·6 per cent) could not then be applied to two separate age groups of under and over 50 years in order to determine the survival benefit of adjuvant systemic therapy. Although the Swedish breast cancer detection results[1] implied that mortality was similar for women under and over 50 years, it appears that the absolute survival benefits (per cent) may well be inaccurate when taking into account the different mortalities for women of different ages.

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Randomized clinical trial of the effect of open *versus* laparoscopically assisted colectomy on systemic immunity in patients with colorectal cancer (*Br J Surg* 2001; 88: 801–7)

Letter 1

Sir

The authors conclude that the systemic immune response is activated equally after both procedures but our previous publications and those from others suggest otherwise. Kloosterman *et al.*[1] first demonstrated significant differences between laparoscopic and conventional cholecystectomy. They studied monocyte human leucocyte antigen (HLA)-DR expression as a parameter for trauma-induced immune suppression. Sietses *et al.*[2] confirmed these results in a randomized clinical study comparing both techniques for Nissen fundoplication. In both studies a significant difference was noticed in postoperative HLA-DR expression on monocytes, favouring the laparoscopic approach. Wakefield *et al.*[3] demonstrated that reduced HLA-DR expression on monocytes and slow restoration to preoperative values after surgical intervention was associated with an increased incidence of infection. These differences, however, were only found 1 day after surgery. The measurements in this trial were performed 3 days after surgery, and probably too late to demonstrate any differences.

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Letter 2

Sir

Wu *et al.* state that several trials had demonstrated significant differences between laparoscopic and conventional surgery and criticized the work of Tang *et al.* because the measurements were performed '3 days after surgery, and probably too late to demonstrate any differences'. Previously only two randomized clinical trials have compared cellular immune function after laparoscopic and conventional colorectal resection. Hewitt *et al.*[1] included only 16 patients and did not show any differences between groups. In a randomized clinical trial performed in our department[2] blood samples were taken on days 1, 2, 4 and 7 after surgery. We did not detect any differences in CD4 and CD8 expression on lymphocytes or CD4/CD8 ratio between the laparoscopic and the conventional group. Human leucocyte antigen (HLA)-DR monocytes were also the same on days 1, 2 and 7. On day 4 a difference in HLA-DR expression on monocytes was detected. An association between surgical infections or sepsis and prolonged HLA-DR monocyte depression for at least 5 days has been described previously[3,4]. Therefore, an HLA-DR monocyte suppression demonstrated on day 4 alone or a depression that is reversed within 2 days of surgery may not be of any clinical relevance.

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Readmissions after pancreatoduodenectomy (*Br J Surg* 2001; 88: 1467–71)

Sir

In order to extrapolate the messages contained within this paper to other healthcare systems, some additional information would be of value.

First, the separation of patients into two categories by type of readmission (complications without tumour and tumour recurrence) seems likely to be difficult to apply at the time that intervention is required and also to preselect a group with longer post-treatment survival in the former category. Patients readmitted for complications such as abscess will not be far along the survival curve and this lag-time phenomenon will select for longer survival in this group.

Second, in what proportion of patients readmitted with tumour recurrence was there a histological diagnosis? Specifically, categories such as readmission with 'general discomfort' were associated with a median survival of 129 days.

Finally, it is not clear from the data whether patients readmitted after pancreatoduodenectomy for adjuvant chemotherapy were planned readmissions or represent a subgroup selected for treatment. The median survival of 395 days in these seven patients is presumably indicative of earlier readmission rather than attributable to adjuvant therapy. This last aspect may indicate differences in healthcare provision. In the UK patients undergoing pancreaticoduodenectomy are usually referred to regional cancer centres for consideration of inclusion in national trials such as ESPAC-3[1] and may not be classified as readmissions.

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Endovascular treatment of abdominal aortic aneurysm: a failed experiment (*Br J Surg* 2001; 88: 1281–2)

Letter 1

Sir

This leading article is to be applauded. Leading vascular surgeons evaluate the experimental data from 10 years and come to the correct conclusion. Who is taking up the challenge?

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Letter 2

Sir

While it is correct to view new technology with a degree of scepticism, we feel the authors are misleading the reader on a number of counts. First, although it is true to say that those abdominal aortic aneurysms less than 5·5 cm in diameter have a low risk of rupture, the natural history of larger aneurysms is not understood[1]. Evidence from the Registry of Endovascular Treatment of Aneuryms suggests that endovascular surgeons in the UK have overwhelmingly chosen to operate on aneurysms greater than 5·5 cm[2]. Results from our own institution indicate the median aneurysm diameter in patients undergoing endovascular aneurysm repair (EVAR) is 6·5 (range 3·2–13·5) cm. Only 12 per cent of patients with aneurysms less than 5·5 cm are operated on. Indeed the majority of patients undergoing EVAR are now part of the national randomized EVAR trials. The EVAR trials, notably ignored by the authors, compare new practice with established practice for aneurysms greater than 5·5 cm. The practice of stenting small aneurysms needs a different study and would be difficult to justify until EVAR is shown to have a mortality rate substantially better than that of controls.

EVAR should be regarded as an evolving technology and be judged accordingly. To abandon a new technology too soon would be wrong. The conversion rate in the early days of laparoscopic cholecystectomy approached 30 per cent in some centres. Such figures are now of historical interest only. The early intervention and correction of perceived problems was commonplace in the initial pilot studies of EVAR. Only now are the criteria for intervention for potential problems, such as type II endoleak, emerging. The latest EVAR devices are far superior to earlier ones. Survival of the fittest is defining which systems are flawed and which have the potential for durable repair. EVAR is no more a failed experiment than the Wright brothers' first aeroplane flight. Both are stories of successful technological advances over time.

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Letter 3

Sir

This article is a masterpiece of selective reporting and misinformation. EUROSTAR publications feature prominently among those that have been picked over. The pan-European EUROSTAR registry was established in 1996 in response to an imperative for reliable and unbiased information on outcomes associated with endovascular aneurysm repair (EVAR). With over 4000 patients registered and a well regulated follow-up programme it is acknowledged to be one of the most important sources of information on EVAR currently available. It is not surprising, therefore, that the authors should turn to it for information upon which to base their article. However, a more balanced review of EUROSTAR publications, and others, discloses that they have (a) underestimated the risk of rupture of untreated aneurysms, (b) underestimated the operative mortality associated with open aneurysm repair, (c) overestimated the operative mortality associated with EVAR, (d) overestimated the mortality risk associated with secondary intervention, and (e) exaggerated the risk of rupture after EVAR.

The jury is still out on the question of whether EVAR should be the treatment of choice for the majority of patients with aortic aneurysms. Collin and Murie fail to mention the ongoing UK EVAR trials. Are they really proposing that the endovascular option should be abandoned before these trials are concluded? To impugn the ethics of clinicians who offer EVAR and the intelligence of patients who choose to accept it does nothing to strengthen their case.

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Letter 4

Sir

Randomized trials are underway in the UK to compare endovascular treatment with open surgery for infrarenal abdominal aortic aneurysms (EVAR trials I and II). Perhaps the authors should have waited for level one evidence to be available before publishing their prejudices. While we agree with some of the statements they make, we are concerned that the therapeutic nihilism expressed against endoluminal treatment of the abdominal aorta may also be applied to pathology of the thoracic aorta.

Endovascular treatment of the thoracic aorta commenced at Stanford in 1992 with home-made stent grafts, just 1 year after Parodi *et al.* published their early experience with stent grafts for the infrarenal aorta[1]. Recent experience with commercially available stent grafts has shown a wide application to thoracic aortic pathology[2]. Diseases that can be treated include acute and chronic dissection, descending thoracic aneurysms, transection and aneurysms related to coarctation. The morbidity and mortality are much reduced when compared with open surgery, as is the incidence of paraplegia[3,4]. Although stent grafts are expensive, the overall cost is reduced because the need for intensive care and a lengthy hospital stay are avoided. Manufacturing companies are constantly refining stent grafts and developing new ones. To suggest that this is a failed experiment is far too premature.

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1 Dake MD, Jiller DC, Mitchell RS, Semba CP, Moore KA, Sakai T. The 'first generation' of endovascular stent-grafts for patients with aneurysms of the descending thoracic aorta. *J Thorac Cardiovasc Surg* 1998; **116:** 689–703; discussion 703–4.
2 Taylor PR, Gaines PA, McGuinness CL, Cleveland TJ, Beard JD, Cooper G *et al.* Thoracic aortic stent grafts – early experience from two centres using commercially available devices. *Eur J Vasc Endovasc Surg* 2001; **22:** 70–6.
3 Keogh BE, Kinsman R. *National Adult Cardiac Surgical Database Report 1998 of the Society of Cardiothoracic Surgeons of Great Britain and Ireland.* London: Concord Services, 1999.
4 Gilling-Smith GL, Worswick L, Knight PF, Wolfe JH, Mansfield AO. Surgical repair of thoracoabdominal aortic aneurysms: 10 years' experience. *Br J Surg* 1995; **82:** 624–9.

Letter 5

Sir

Working in a peripheral district general hospital with a moderate endovascular aneurysm repair (EVAR) practice (26 in 37 months), we wish to stress several points. There are potentially beneficial outcomes from EVAR: significantly lower blood loss, shorter duration of hospitalization, and reduced rate of cardiac and pulmonary complications[1]. The increase in technology has seen grafts and stents superseded and inferior stents replaced. Assessment of patient outcome needs to take into account the lag effect following withdrawal of an inappropriate endograft and it will be several years before we see adjusted survival data for current grafts. We were interested that ongoing randomized clinical trials using current endografts, comparing open surgery and EVAR (EVAR I), and comparing best medical management and EVAR in the surgically unfit patient (EVAR II), were not mentioned. Surely we should await the outcome of well-run trials before changing practice? With open abdominal aortic aneurysm (AAA) repair, mortality rates have decreased from 13 per cent in 1955–1965 to 8·4 per cent in 1966–1973, to less than 4 per cent today[2]. These extraordinarily high death rates did not influence surgeons to abandon the technique. It has been shown previously that EVAR is suitable in only 30 per cent of patients with AAA[3], but with improving technology the potential for application of these techniques in patients with ruptured AAA (to reduce the high mortality rate) must be worth investigating.

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1 Hicks GL, Eastland MW, DeWeese JA, May AG, Rob CG. Survival improvement following aortic aneurysm resection. *Ann Surg* 1975; **181:** 863–9.
2 Becquemin J, Bourriez A, D'Audiffret A, Zubilewicz T, Kobeiter H, Allaire E *et al.* Mid-term results of endovascular *versus* open repair for abdominal aortic aneurysm in patients anatomically suitable for endovascular repair. *Eur J Vasc Endovasc Surg* 2000; **19:** 656–61.
3 Woodburn KR, Chant H, Davies JN, Blanshard KS, Travis SJ. Suitability for endovascular aneurysm repair in an unselected population. *Br J Surg* 2001; **88:** 77–81.

Letter 6

Sir

We feel that the views expressed by the authors are premature. We have been carrying out endovascular repair since 1994, initially using a home-made device for which long-term results are now available and will be published shortly. The long-term primary success rate was 79 per cent at 6 years. Twenty per cent of these patients required secondary interventions but these were mainly distal endoleaks, which were easily dealt with. The bifurcated grafts we have used recently have caused few problems apart from type 2 endoleaks. These are usually insignificant unless the sac increases in size, which rarely occurs. We dispute the statement that technical feasibility of endoluminal repair decreases with increasing diameter. In our own series the mean diameter of the sac was 6 cm. Recently we have been operating on patients with wider necks without obvious problems.

The feasibility of endovascular treatment of abdominal aortic aneurysms (AAAs) is now established and we must try to find its place in the treatment of AAAs. It is inappropriate to issue verdicts on this method of treatment when it is widely known that a randomized trial has been funded and is in progress in the UK. Until the results of this trial are available, the answer will remain unknown. Surely it is better to wait for truly scientific evidence before reaching a conclusion? Their approach provides more ammunition to those who criticize surgical research.

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Authors' reply

Sir

Harris and Buth make five unsubstantiated allegations. In our view:

(a) the risk of rupture of untreated abdominal aortic aneurysms (AAAs) less than 5·5 cm in anteroposterior diameter measured by ultrasonography is less than 1 per cent per annum[1]. For AAAs of 5·5–6·4 cm in diameter it is unknown but probably less than 5 per cent per annum.
(b) the 30-day all-centres UK operative mortality rate for open AAA repair is unknown. Volunteered data from 177 participating hospitals revealed an in-hospital mortality for non-ruptured aneurysm surgery of 7·1 per cent[2].
(c) the 30-day all-centres operative mortality rate for endovascular aneurysm repair (EVAR) is unknown but the probable median is around 5 per cent.
(d) the 30-day all-centres operative mortality rate for open AAA repair after failed EVAR is unknown but is probably around 20 per cent.
(e) there is no evidence to support the belief that the rate of AAA rupture after EVAR is substantially less than that of untreated AAAs of the same size.

If Harris and Buth have data to refute our estimates they should be disclosed. Surgical coyness is quaint but unhelpful.

The concern of Taylor *et al.* was predictable but our article made no reference to thoracic aortic aneurysms. If EVAR for thoracic aortic aneurysms substantially reduces the risk of aneurysm rupture with acceptable operative mortality and morbidity rates, it may have a place in prophylactic therapy. If the evidence were available it could be considered.

The experience of Ingle and Bell, that technical feasibility of endoluminal repair does not decrease with increasing aneurysm diameter, is unique and fantastic. We note that for EVAR in Leicester the mean diameter of the aneurysm was 6 cm while in Nottingham only 12 per cent of aneurysms were less than 5·5 cm in diameter. We assume they quote maximum diameters in any plane measured by computed tomography. We presume therefore that, in Leicester, more than half and, in Nottingham, more than a quarter of all patients undergoing EVAR have aneurysms with maximum anteroposterior diameters measured by ultrasonography of less than 5·5 cm.

Five letters suggest our conclusions are premature and refer to the EVAR I and EVAR II trials in progress. When the trial data are published they can be considered. We cannot predict the future but our present observations are:

(a) Inclusion in the trials is based on maximum AAA diameter measured by computed tomography not anteroposterior diameter measured by ultrasonography.
(b) EVAR I has no best medical treatment control group for AAA diameters of less than 6·5 cm measured by computed tomography or less than 6·0 cm anteroposteriorly measured by ultrasonography.
(c) Recruitment to EVAR II has been much slower than predicted from the number of patients who, before the trial began, had been having EVAR because they were said to be unfit for open surgery.

The gestation period of experimental endovascular treatment of AAA has already been 10 years. Induction is long overdue. When eventually delivered, it will probably be stillborn. We believe it is dead already.

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1 The UK Small Aneurysm Trial Participants. Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. *Lancet* 1998; **352:** 1649–55.
2 Bayly PJ, Matthews JN, Dobson PM, Price ML, Thomas DG. In-hospital mortality from abdominal aortic surgery in Great Britain and Ireland: Vascular Anaesthesia Society audit. *Br J Surg* 2001; **88:** 687–92.

Book reviews

Surgery: Scientific Principles and Practice. 3rd Ed.

L. J. Greenfield, M. W. Mulholland, K. T. Oldham,
G. B. Zelenock and K. D. Lillemoe

285 × 220 mm. Pp. 2381. Illustrated. 2001. Philadelphia, Pennsylvania: Lippincott Williams and Wilkins. $149·00.

This book contains 2381 pages, all of them in tight type with monochromatic figures and the appearance of a rather dated style. I found it heavy going and a bit of a struggle to get into or to get a great deal from. I am sure the information is all there and I am equally sure that it is of very high quality but, in terms of the accessibility, it is not on the easy side of the scale. The individual sections in relation to specialty are of interest to the appropriate specialists but the work might better have been published as a number of separate volumes dealing with various aspects of scientific principle and surgical practice, as opposed to appearing all in one huge tome. I believe this book is not general enough to satisfy the generalists and covers far too many fields to satisfy the specialists. I cannot really recommend it to anyone save as an impressive tome with an impressive title.

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Breast Cancer: A Practical Guide. 2nd Ed.

O. E. Silva and S. Zurrida (eds)

210 × 140 mm. Pp 542. Illustrated. 2000. Amsterdam: Elsevier Science. US$43·00.

This soft-back book is written in outline note form in order that it may be used as a bedside reference. Despite multi-authorship, the format is consistent. The reader can rapidly locate a particular area of interest and is given an up-to-date synopsis of the facts supported by the data from relevant high-quality peer-reviewed articles. There are sufficient factual data, clearly expressed, to help the clinician, whether oncologist, surgeon or radiologist; the information given with the references is succinct and enables the reader to evaluate the importance of any individual reference. In addition to the usual index, there is an appendix which includes comprehensive 'contents' including references. This means that the reader can refer to a specific trial or can obtain an overview on a topic, such as breast conservation surgery, where established facts, important historical developments and up-to-date trial results are listed. This is an excellent way for clinicians to keep up to date with ease, secure in the knowledge that the facts are well presented and accurate.

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Textbook of Endovascular Procedures

J. F. Dyet, D. F. Ettles, A. A. Nicholson and
S. D. Wilson

285 × 220 mm. Pp 501. Illustrated. 2000. Edinburgh: Churchill Livingstone. £145·00.

This book is aimed primarily at vascular specialists who have an interest in endovascular treatment. The author list is impressive, comprising world renowned vascular surgeons, radiologists and physicians. It is logically set out with sections on basic principles, arterial and venous interventions, embolization procedures and endovascular grafts. Each chapter has been jointly written by radiologists and surgeons which unfortunately has led to some duplication. There are excellent sections on renal and visceral artery techniques, and abdominal and thoracic aortic disease. In addition to the expected information it also covers topics such as medicolegal issues and advice on how to retrieve intravascular foreign bodies. There are good illustrations throughout and these complement the text. This volume is unique in that it presents both the radiological and surgical perspective on most subjects. It is aimed at the modern vascular specialist, but many surgeons will probably feel that radiology has been over represented. It is well written and full of up-to-date information with no obvious oversights. It is primarily a reference book for surgeons, radiologists and trainees with an interest in endovascular techniques.

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Sabiston Review of Surgery

C. M. Townsend Jr, R. D. Beauchamp, K. L. Mattox
and B. M. Evers (eds)

275 × 210 mm. Pp 167. Not Illustrated. 2001. Philadelphia, Pennsylvania: WB Saunders. US$39·95.

The *Sabiston Textbook of Surgery* (derived from the *Christopher Textbook of Surgery* of 1936) has long been the bible of surgery for medical students, residents, surgeons and medical school teachers, not only in USA but worldwide. All authors are traditionally distinguished experts in their field and the 16th edition was published in the first year of the new century. Based on this new edition, Professor Townsend and his associates have collected more than 1200 review questions prepared by authorities, from which 533 were adopted in the *Sabiston Review of Surgery*. To write this book review, I have solved all the questions. Although there are several that seem specific to the USA, most are applicable worldwide. For each question, rationales for the correct answer are fully described. Page numbers in the *Sabiston Textbook of Surgery* are also given for each question so that self-directed study of particular subjects can be carried out efficiently. *Sabiston Review of Surgery* is a comprehensive teaching device that assures the reader an accurate, up-to-date, knowledge of surgical science. It will be particularly useful for medical students, surgical trainees and others who are preparing for professional examinations.

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Vascular and Endovascular Surgical Techniques. 4th Ed.

R. M. Greenhalgh (ed.)
280 × 222 mm. Pp 548 Illustrated 2001 Philadelphia, Pennsylvania. WB Saunders £99·95

This book is the latest in a series produced to accompany the annual Charing Cross Hospital Symposium held in London. The 23rd meeting addressed the topic of 'Vascular and Endovascular Techniques' and the chapters within this volume are written by the speakers at the symposium. Inevitably with a book of this nature, production time is limited and tight editing is never completely possible. I mention this because, whereas the majority of chapters are extremely well written and reflect modern vascular and endovascular surgical practice, a few fall short of the mark. I do not believe that any of us still use intraluminal 'home-made' plastic shunts during carotid endarterectomy or identify perforating lower limb veins using clinical examination alone. Although these views are published as written, editor's notes are used with discretion as appropriate.

The chapter headings are well researched and book structure generally respected. No results are given and the reader must be aware that several of the procedures described are not widely practised due to suboptimal outcome, i.e. venous valve surgery. This aside, the majority of the text is well presented and topical. The illustrations are excellent. The field of interventional surgery continues to advance and it is of interest that many of the aortic stent graft types presented have since been withdrawn. In addition, there is no chapter detailing specifically the management of aortic stent graft dysfunction (excluding endoleak). The reader will have to await the publication of the 2002 book to fully appreciate the problems encountered in the introduction of the latest techniques and the evidence for their continued use.

In summary, this is an excellent book that definitely fills a gap in the market. It is ideal for those involved with both vascular and endovascular surgical techniques, and provides a glimpse into the future as well as an appreciation of the past. I have enjoyed the read and would recommend it as a valuable addition to the library of any specialists involved in modern vascular practice.

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Dialysis Access: Current Practice

J. A. Akoh and N. S. Hakim (eds)
220 × 160 mm. Pp 400 Illustrated 2001 London: World Scientific Publishing £50.00.

This is a multi-contributor book about dialysis access and both vascular and peritoneal access are covered. The book is 400 pages long but is about the right size for a text attempting to provide a definitive account for a relatively small readership. Regarding the list of contributors, there is clearly an intention to encompass practice on both sides of the Atlantic. However, access is one area where Europeans occupy the high ground, with national guidelines in the USA being introduced to drive practice towards the European perspective. Hence, the book loses some of its identity with its most likely target audience.

As is often the case with multi-author books there is a lot of repetition and the chapters do not seem to flow in a logical order. The chapter on peritoneal dialysis is a poor orphan and I wonder whether the editors are really committed to discussing this area. Despite these criticisms, there are many excellent chapters on vascular access in this book that alone make it worth reading. I look forward to the second edition; given some draconian editorial pruning it should be a worthy contributor to this field.

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Endocrine Surgery: A Companion to Specialist Surgical Practice. 2nd Ed.

J. R. Farndon (ed.)
250 × 190 mm. Pp 319. Illustrated. 2001. London: WB Saunders. £49·95.

The design of this series, as stated in the preface by the series editors, is to meet the needs of the higher surgical trainee and busy practising surgeon, and to provide up-to-date information on recent developments within each subspecialty of surgical practice. This has been fulfilled in this volume on endocrine surgery. The detachment of endocrine from breast surgery as a stand-alone volume in this second edition meets both demand and expectations. Each chapter is clearly written and well illustrated. The incorporation and highlighting of evidence-based practice in surgery, with the inclusion of many updated references, are valuable to the reader. The chapters on clinical governance and quality in endocrine surgery, as well as medicolegal aspects, are practical and useful but may not be readily appreciated by readers outside the UK. In addition, the inclusion of the chapter on the salivary gland seems to be out of context in this volume. Nevertheless, all relevant topics in endocrine surgery have been covered succinctly. This book serves to bridge the gap in knowledge with regard to endocrine surgery that is currently obvious in general surgical textbooks.

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Breast Surgery: A Companion to Specialist Surgical Practice. 2nd Ed.

J. R. Farndon (ed.)
224 × 160 mm. Pp 383. Illustrated. 2001. London: WB Saunders. £49·95.

With such a plethora of detailed texts available on the management of breast disease there was a need for a clear and concise text aimed at the breast surgeon. This new volume on breast surgery from the *Companion to Specialist Practice* series largely hits the spot. Its ten chapters cover the core curriculum required for the surgeon specializing in breast disease. John Farndon has generally achieved that essential editor's goal of ensuring that all the contributions are stylistically similar. I found the chapters on breast screening, the treatment of early stage breast cancer, palliative care in breast cancer and litigation in breast disease particularly readable and informative. Perhaps a minor criticism in a text of limited scope is that a little too much space was dedicated to the subject of breast cancer in men, even though the chapter itself is well written. A separate chapter on breast reconstruction and cosmetic breast surgery may have been more useful. As with all multi-author texts there is a certain amount of repetition from chapter to chapter, but this serves to reinforce important points and is not in any way distracting. Breast disease is such a rapidly changing field of medical practice that even a book conceived and constructed in 2000 can appear slightly out of date in 2002. Where new evidence has come to light at the time of publication a possible solution is to ask each chapter author to add a short addendum to the end of their contribution to point out the most recent evidence. I can recommend this book to all surgical trainees subspecializing in breast surgery and to all consultants striving to keep up to date.

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Vascular and Endovascular Surgery: A Companion to Specialist Surgical Practice. 2nd Ed.

J. D. Beard and P. A. Gaines (eds)
250 × 190 mm. Pp 546. Illustrated. 2001. London: WB Saunders. £59·95.

This book is one of the eight companion texts in the excellent *Specialist Surgical Practice* series that was first published in 1997. Differences between the first and second editions of *Vascular and Endovascular Surgery* are an increase in pages, from 494 to 546, and an increase in chapters, from 17 to 20. All of the original retained chapters have been extensively revised and updated. New chapters include 'Amputation – Rehabilitation and Prosthetic Developments', 'Endovascular Management of Aortic Aneurysms and Dissections', and 'Thrombophilia and the Management of Complex Thromboembolism'. The previously combined chapter, 'Vascular Grafts, Sutures, Anastomoses, and Angioplasty and Stents' has been separated into two distinct chapters. The authorship has increased from 31 to 37 contributors, all of whom are from the UK except for one who is from Australia. The text is co-edited by a vascular surgeon and an interventional radiologist. The spectrum of the book covers the complete gamut of what a modern day vascular surgical practice should encompass.

The editors have achieved their goal of providing an affordable, up-to-date, specialist text, although it is definitely not a substitute for a comprehensive textbook of vascular surgery. However, the book contains an important amount of current information which would be invaluable to individuals managing patients with peripheral vascular disease. There are occasional gaps in the information presented, such as the management of a patient with a history of knee dislocation. The authors have also attempted to incorporate information concerning evidence-based practice in vascular disease and endovascular surgery throughout the text, and have highlighted relevant references. This is a useful exercise that underlines the general lack of evidence-based information available. The chapters are easy to read, and there is minimal overlap of information. This should be an essential text for vascular trainees and for those who require up-to-date information on the management of vascular disease.

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Handbook of Venous Disorders. 2nd Ed.

P. Gloviczki and J. S. T. Yao (eds)
275 × 200 mm. Pp 557 Illustrated. 2001. London: Arnold. £95.00

This second edition is an update in the light of progress made during the past 5 years. It has almost 90 contributors who are mainly from the USA. Like any such book, the quality of the contributions ranges from excellent to disappointing and there is repetition. To a degree this does not matter because some topics can, with profit, be read in isolation and on their own merits. None the less, more vigilant editing could have reduced the duplication considerably and the chapter formats could have been standardized. The style of the volume is didactic and tends to reflect the sometimes incompletely argued preferences and prejudices of particular authors; the concept of management is almost universally interventional. What is lacking is a balanced and critical assessment and a focus on practical clinical topics. For instance, the reader will not find scientifically based arguments for or against calf perforating vein ligation, or on how to manage a leg ulcer. In summary, while there are many superb and invaluable chapters, in general the book would benefit from vigorous editing and the adoption of a more critically balanced and focused style.

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Endovascular Therapy for Atherosclerotic Renal Artery Stenosis: Present and Future

M. R. Jaff (ed.)
280 × 180 mm Pp 160. Illustrated. 2001. Armonk, New York: Futura. US$75·00

There are relatively few recently published books on renovascular disease and this text provides a comprehensive summary of the current literature on atherosclerotic renal artery stenosis (ARAS). There are excellent chapters on the prevalence and clinical manifestations of ARAS as well as an up to date, but short, chapter on radiological assessment with appropriate diagnostic algorithms. Chapters on the technical aspects of endovascular intervention provide useful tips but omit discussion of the treatment of stent restenosis. There is a chapter on the surgical treatment of ARAS with interesting discussion of the relative benefits of endovascular *versus* operative intervention. Each chapter is well written and has appropriate illustrations and extensive references, and each expert offers a slightly different approach to a controversial subject. This causes some unfortunate overlap between chapters, particularly in relation to prevalence and clinical assessment. Several chapters describe the results and experience of a single centre; these are less helpful than more general discussions. Overall, I recommend this book to radiologists, physicians and surgeons with an interest in ARAS. It is an excellent overview of current knowledge regarding clinical assessment, diagnosis and therapeutic options.

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Scientific Surgery

Warren BL, Eid A, Singer P, Pillay SS, Carl P, Novak I *et al.* High-dose antithrombin III in severe sepsis. A randomized controlled trial. *JAMA* 2001; **286:** 1869–78.

A total of 2314 patients were treated within 6 h of the onset of severe sepsis. After 28 days, there was no significant reduction in overall mortality: 38·9 per cent antithrombin III, 38·7 per cent placebo.

Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8507 patients from 22 randomized trials. *Lancet* 2001; **358:** 1291–304.

Preoperative radiotherapy reduced the rate of local recurrence by 46 per cent and the late mortality rate from 50 to 45 per cent. Postoperative radiotherapy also reduced the rate of local recurrence, but by 37 per cent.

Shukla VK, Ojha AK, Pandey M, Pandey BL. Pentoxifylline in perforated peritonitis: results of a randomised, placebo controlled trial. *Eur J Surg* 2001; **167:** 622–4.

The 36 patients mostly had typhoid or duodenal ulcer perforations. Pentoxifylline for 3 days after surgery significantly reduced median postoperative hospital stay (8 *versus* 11 days, $P = 0{\cdot}02$) and the wound infection rate (six of 18 *versus* 12 of 18, $P = 0{\cdot}02$).

Koda M, Murawaki Y, Mitsuda A, Oyama K, Okamoto K, Idobe Y *et al.* Combination therapy with transcatheter arterial chemoembolization and percutaneous ethanol injection compared with percutaneous ethanol injection alone for patients with small hepatocellular carcinoma. A randomized control study. *Cancer* 2001; **92:** 1516–24.

Combination therapy worked best for small tumours of less than 2 cm diameter in this study including 52 patients. At 3 years it significantly reduced the rate of residual disease (19 *versus* 39 per cent, $P = 0{\cdot}01$), but had no effect on survival (81 *versus* 66 per cent, *P* not significant).

Sargent DJ, Goldberg RM, Jacobson SD, Macdonald JS, Labianca R, Haller DG *et al.* A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. *N Engl J Med* 2001; **345:** 1091–7.

The analysis included 3351 patients from seven trials. Chemotherapy significantly improved overall survival (hazard ratio 0·76, 95 per cent confidence interval (c.i.) 0·68 to 0·85) and reduced recurrence (hazard ratio 0·68, 95 per cent c.i. 0·6 to 0·76). The effects were similar in patients over and under 70 years old.

Ros A, Gustafsson L, Krook H, Nordgren C-E, Thorell A, Wallin G *et al.* Laparoscopic cholecystectomy *versus* mini-laparotomy cholecystectomy. A prospective randomized single-blind study. *Ann Surg* 2001; **234:** 741–9.

A total of 724 operations were studied. There was no difference in complication rates (one bile duct injury in each group). Hospital stay and convalescence was shorter after laparoscopic cholecystectomy.

Caparros T, Lopez J, Grau T. Early enteral nutrition in critically ill patients with a high-protein diet enriched with arginine, fibre, and antioxidants compared with a standard high-protein diet. The effect on nosocomial infections and outcome. *JPEN J Parenter Enteral Nutr* 2001; **25:** 299–308.

Some 222 patients from 15 intensive care units were included. The enriched high-protein feed reduced the risk of catheter-related sepsis, but did not affect mortality or length of stay.

Neoptolemos JP, Stocken DD, Dunn JA, Almond J, Beger HG, Pederzoli P *et al.* Influence of resection margins on survival for patients with pancreatic cancer treated by adjuvant chemoradiation and/or chemotherapy in the ESPAC-1 randomized controlled trial. *Ann Surg* 2001; **234:** 758–68.

Some 541 patients were studied. Positive resection margin influenced outcome (median survival 10·9 months *versus* 16·9 months for clear margins). There was a survival benefit from chemotherapy, but not chemoradiation, regardless of margin status.

Bonneterre J, Buzdar A, Nabholtz J-MA, Robertson JFR, Thurlimann B, von Euler M *et al.* Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma: results of two randomized trials designed for combined analysis. *Cancer* 2001; **92:** 2247–58.

These two trials enrolled 1021 postmenopausal women. Results with anastrozole were slightly better – complete or partial response 29 per cent *versus* 27·1 per cent, and clinical benefit rates 57 *versus* 52 per cent. Both were well tolerated but anastrozole led to fewer thromboembolic complications ($P = 0{\cdot}04$).

Bozzetti F, Braga M, Gianotti L, Gavazzi C, Mariani L. Postoperative enteral *versus* parenteral nutrition in malnourished patients with gastrointestinal cancer: a randomized multicentre trial. *Lancet* 2001; **358:** 1487–92.

This multicentre trial enrolled 317 patients. Enteral nutrition reduced the rate of postoperative complications (34 *versus* 49 per cent, $P = 0{\cdot}005$) and length of hospital stay (13·4 *versus* 15 days, $P = 0{\cdot}009$), but 9 per cent had to switch to parenteral feeding and adverse events from feeding were more frequent (35 *versus* 14 per cent, $P < 0{\cdot}001$).

Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324:** 71–86.

This updated analysis considered 287 studies involving 135 000 patients. It strengthened the message that antiplatelet therapy is protective in most types of patient at risk of occlusive vascular events.

The *BJS* website can be found at *http://www.bjs.co.uk*. In addition to details of current and previous articles featured in Scientific Surgery, the website contains details of the Editorial Team and Board, instructions to prospective authors, links to other sites (such as The Cochrane Library) and forthcoming surgical events. The Editors welcome comments and suggestions about the website, either in writing or through the website address.

Vascular Surgical Society of Great Britain and Ireland abstracts

The following abstracts are from the papers presented at the 35th Annual Scientific Meeting of the Vascular Surgical Society of Great Britain and Ireland, held in Brighton, UK on 7–9 November 2001. President of the Society, Mr R. N. Baird, was in the Chair.

Systematic review of stripping of the long saphenous vein in varicose vein surgery

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Background: Practice varies regarding stripping of the long saphenous vein (LSV) during varicose vein surgery. A systematic review has been carried out according to Cochrane Collaboration guidelines to examine evidence relating to this practice.

Methods: All randomized controlled trials of LSV stripping were identified by systematic searching of 38 electronic databases and hand-searching of relevant journals. Studies were critically appraised for inclusion, based on predetermined quality criteria. Dual data extraction was carried out and, where appropriate, results were combined using meta-analysis.

Results: Of 26 papers identified, 14 studies met the quality criteria. Differences in reporting methods and outcomes precluded statistical meta-analysis. Two trials (four papers) compared stripping to the knee *versus* no stripping. One showed no significant difference in complications, but a reduced 2-year recurrence rate and 5-year reoperation rate following stripping. The second confirmed better objective and subjective results following stripping. Nerve damage was increased by stripping upwards rather than downwards (one study) and from stripping to the ankle rather than the knee (one study). Two studies compared standard and invagination stripping, with no significant difference apart from a shorter exit wound length following invagination. Studies of plastic *versus* metal strippers, stripping *versus* sequential avulsions, and stripping *versus* perforator ligation showed no differences in complications or outcomes.

Conclusion: Systematic review of the literature suggests that stripping of the LSV downwards from groin to knee results in a lower recurrence rate without significant added morbidity and should be accepted as standard practice. Invagination stripping may reduce wound length, but other variations in technique have not demonstrated significant benefits.

Case mix in recruitment to a randomized controlled trial of varicose vein treatment

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Background: Varicose veins are a common problem and a major component of surgical waiting lists. Purchasers have attempted to ration the treatment of varicose veins although the effectiveness and cost-effectiveness of available treatments have never been tested adequately in randomized controlled trials (RCTs). Such RCTs are difficult owing to lack of clinical equipoise and patients' expectations for treatment.

Methods: The REACTIV trial combines RCTs, observational data collection and economic modelling to assess the cost-effectiveness of treatments for varicose veins. Consecutive patients referred to two participating vascular units were recruited to three randomized arms of the trial. Those excluded or who declined randomization were asked to participate in an observational study to collect parallel data.

Results: Over a 2-year interval 1004 consecutive patients were recruited; 106 were excluded from randomization under the trial protocol. Of 898 eligible for the randomized study, 312 agreed to randomization. Analysis of initial recruitment showed significant differences between randomized and non-randomized patients. Differences included symptoms and anatomical distribution of veins, trial centre, smoking history, previous sclerotherapy or phlebitis, obesity, and family history of ulceration.

Conclusion: Although RCTs are considered the 'gold standard' for evidence, difficulties in recruiting patients to surgical trials of established treatments may result in potential bias. This may be partially overcome by collecting observational data in excluded patients, modelling projected outcomes and using sensitivity analysis, thus expanding the applicability of RCT results.

Inhibition of experimental venous thrombosis with a human anti-factor VIII monoclonal antibody

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Introduction: Factor VIII (FVIII), an essential cofactor of blood coagulation, has been associated with the development of venous thrombosis. A human high-affinity monoclonal antibody (mAb-LE2E9) has been made against FVIII that only partially inhibits its procoagulant activity, even in excess. The aim of this study was to evaluate the antithrombotic effect of this antibody in a mouse model of deep vein thrombosis.

Methods: A flow model of venous thrombosis was used in haemophilic mice (FVIII gene deleted). Two groups of mice ($n = 14$), reconstituted with human FVIII, were injected intravenously with either the antibody or saline before thrombus induction. Thrombus was also induced in a third group of mice ($n = 6$) which were not reconstituted with FVIII. Thrombi were harvested at 4 h, sectioned at fixed intervals and stained. Thrombus size was estimated by scoring seven sections for the presence or absence of thrombus (score of 1 or 0 respectively). Scores were summed for each animal.

Results: Mice reconstituted with FVIII showed no signs of perioperative haemorrhage. Ten of 14 mice receiving saline *versus* one of 14 mice receiving the antibody developed a thrombus ($P = 0{\cdot}001$, Fisher's exact test). Median (interquartile range) thrombus size was 6 (0–7) and 0 (0–0) for control and treated animals respectively ($P = 0{\cdot}006$, Mann–Whitney U test). Haemophiliac mice not reconstituted with FVIII died from haemorrhage and did not have thrombus.

Conclusion: The human anti-FVIII monoclonal antibody mAb-LE2E9 significantly reduced the risk of venous thrombosis without the risk of haemorrhage. This antibody could be useful as an antithrombotic agent.

The day-case unit is the key to basic surgical training

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Background: The Royal College of Surgeons recommends that 50 per cent of all surgical operations should be performed as a day case. Professional guidelines advise that this surgery should be carried out by consultants. The authors conducted a study to analyse the contribution of the day-case unit (DCU) to basic surgical training on a vascular unit.

Methods: The logbooks of five basical surgical trainees were analysed between 1998 and 2000, looking for exposure to varicose vein and vascular access surgery, and progression to amputation and bypass surgery during each trainee's 6-month attachment. Surgeons in their first senior house officer (SHO) post (group 1) were compared with those in their second or subsequent post (group 2).

Results: The mean(s.d.) operative caseload was 273(41). Emergency work comprised 15(7) per cent and day-case surgery 35(3) of workload. A mean(s.d.) of 66(5) varicose vein and access cases was undertaken on the DCU, accounting for 82 per cent of day-case experience. SHOs were involved in 20(11) operations as first assistant, and performed 35(5) with senior assistance and 12(6) unassisted. All progressed to perform limb amputation and the femoral component of lower-limb bypass (under supervision) during their time on the unit. There was no difference in operating experience or progression to major surgery between the groups.

Conclusion: Vascular surgical firms can provide a good introduction to surgical skills. Most first operator experience was gained on the DCU. Consideration should be given to formal DCU placements early in surgical training.

Surgical technique and preliminary results of transluminal occlusion of perforator veins

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Background: The aim was to describe and report early results of a new technique of minimally invasive treatment of incompetent perforating veins (IPVs), called TRLOP (TRansluminal Occlusion of Perforators).

Methods: Between December 2000 and July 2001, consecutive patients undergoing varicose vein surgery with IPVs consented to an observational study looking into the feasibility of using a minimally invasive VNUS Closure (VNUS Medical Technologies, San Jose, California, USA) technique to ablate IPVs. All patients had preoperative ultrasonography of the venous anatomy and calf perforator status was defined. At operation, once the long saphenous had been dealt with, IPVs were cannulated under ultrasonographic guidance using a 14-G Abocath. A 5-Fr VNUS closure catheter was passed through the cannula and into the IPV. Radiofrequency current was then passed through the catheter under local pressure, resulting in destruction of the vein wall and closure of the perforator. On-table duplex ultrasonography was used to confirm closure of the IPV and for follow-up imaging.

Results: Thirty-five patients (46 legs) have so far undergone the procedure (27 women and eight men; mean age 55 (range 34–78) years). A total number of 78 IPVs (range 1–3 per leg) was treated. All IPVs were found to have closed at operative and follow-up scans (up to 6 months), with no visible blood flow.

Conclusion: TRLOP is a new minimally invasive technique that appears to be effective in the treatment of IPVs. If proven by further studies, it may replace open and subfascial endoscopic perforator vein surgery.

Persistent popliteal fossa duplex reflux following saphenopopliteal disconnection

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Background: This study was a retrospective assessment of the technical adequacy of surgical saphenopopliteal disconnection (SPD).

Methods: Patients undergoing SPD had preoperative colour-coded duplex imaging to localize the saphenopopliteal junction and analyse the popliteal venous anatomy. A single consultant vascular surgeon performed all scans and SPD procedures. Patients were rescanned 6 weeks after operation.

Results: Fifty-eight patients (24 men and 34 women; median age 54 years) underwent SPD over a 4-year interval. There were seven staged bilateral procedures. Complete data were available for 51 patients. Based on postoperative duplex scans, patients were divided into four groups: 'ideal' – incompetent saphenopopliteal junction successfully disconnected without residual superficial vein reflux (39 per cent); 'satisfactory' – an incompetent junction was disconnected successfully but with persisting superficial venous reflux (24 per cent); 'duplex failure' – a previously identified incompetent junction persisted but was found to be competent (10 per cent); and 'surgical failure' – an incompetent junction was completely missed during surgery (27 per cent). Two major complications (4 per cent) occurred in this series (one deep vein thrombosis and one popliteal vein injury) and one patient suffered sural nerve palsy.

Conclusion: Despite preoperative duplex localization of the saphenopopliteal junction and surgical specialization, SPD is an unreliable technique. It also risks major complications. The authors question the role of SPD for cosmetic varicose veins and, by extension, the value of re-do SPD for any indication.

Significance of aneurysm thrombus in endovascular aortic aneurysm repair

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Background: Aneurysm thrombus remains an uncertain entity in endovascular aortic aneurysm repair (EVAR). The aim of this study was to determine the relevance of aneurysm thrombus to the risk of complications after EVAR.

Methods: Anatomical data for 3414 patients who underwent EVAR from January 1994 to June 2001 were evaluated. The maximal aortic diameter and the mean luminal diameter were measured, and the thickness of aneurysm thrombus was calculated by subtraction. The thickness was proportional to the volume of thrombus in the aneurysm sac. This was then correlated with common complications of EVAR (endoleak, kinking, thrombosis, migration, rupture, conversion to open repair and aneurysm-related death). Data are reported as mean(s.d.), and were analysed with the Mann–Whitney *U* test and life regression analysis.

Results: The thickness of aneurysm thrombus was decreased in patients with overall endoleak ($n = 636$) (16·6(11·8) *versus* 19·3(11·9) mm for those without endoleak; $P < 0{\cdot}001$) and this remained significant after correction for follow-up ($P < 0{\cdot}001$). Thrombus thickness was smaller for patients with a distal endoleak ($n = 183$) (15·2(11·5) *versus* 19·0(11·9) mm for those without endoleak; $P = 0{\cdot}001$) and remained significant for the duration of follow-up ($P = 0{\cdot}011$). However, increased thickness of thrombus (20·0(12·3) *versus* 18·6(11·8) mm; $P = 0{\cdot}001$) was associated with aneurysm-related death ($n = 352$) when corrected for duration of follow-up.

Conclusion: Decreased volume of aneurysm thrombus was related to increased risk of endoleak; however, the risk of aneurysm-related death was associated with a greater thickness of aneurysm thrombus.

Fast growth in diameter does not justify precocious abdominal aortic aneurysm repair

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Background: Growth of abdominal aortic aneurysm (AAA) diameter of 1 cm per annum or more is claimed to be an indication for repair. The validity of this claim was investigated.

Methods: Between January 1988 and October 2000, 277 patients have had duplex ultrasonography at 6-monthly intervals in an aneurysm surveillance programme. During this interval, fast growth was not an indication for operation in this unit.

Results: The mean aneurysm growth rate was 0·2 cm per 6 months. The upper 95th centile was 0·5 cm per 6 months, i.e. 1·0 cm per annum. There were 63 patients whose aneurysms had grown 0·5 cm or more in 6 months. Thirty-three of the 63 patients had an aneurysm measuring 5·5 cm or greater in anterior–posterior diameter in consequence of the fast growth and all have been either operated on or deemed not fit owing to anaesthetic risk. The remaining 30 patients continued in surveillance for a total of 50 patient-years and none had rupture of the aneurysm. The upper 95 per cent confidence interval for risk of rupture was 6 per 100 patient-years. Fifteen of the 30 patients had not been operated on and three patients had died from unrelated causes by the end of the study.

Conclusion: These data support the view that a rapid increase in AAA diameter is not an indication for surgery.

Does supervised exercise for intermittent claudication affect the cardiac risk profile? Results of a randomized controlled trial

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Background: Patients with intermittent claudication suffer enhanced cardiovascular and cerebrovascular morbidity and mortality. The aim of this study was to investigate the effect of exercise training on cardiac risk factors and inflammatory markers.

Methods: Patients with stable symptoms of intermittent claudication were randomized to either 3 months of supervised exercise or a control group receiving exercise advice alone. All patients continued their current medication without dose modification. Patients were assessed before randomization and at 3 and 6 months when fasting blood samples were taken for measurement of lipid profile, homocysteine, glucose, haemoglobin A1c, C-reactive protein (CRP) levels and plasma viscosity. Neutrophil CD11b expression before and after treadmill exercise was measured by flow cytometry of fluorescein isothiocyanate-labelled whole blood.

Results: Fifty-two patients were randomized, of whom 48 were successfully followed to 3 months. Supervised exercise favourably modified the fasting lipid profile compared with controls, with a relative increase in high-density lipoprotein (HDL) cholesterol (median 7·1 (interquartile range (i.q.r.) 0·0 to 9·9) per cent) and reduction in low-density lipoprotein cholesterol (median −5·3 (i.q.r. −11·7 to 7·6) per cent). This produced a significant reduction in total/HDL cholesterol in the supervised group compared with controls (−5·5 *versus* 2·0 per cent; $P = 0{\cdot}01$, Mann–Whitney U test). No significant changes in fasting levels of triglycerides, total cholesterol, blood glucose, HbA1c, homocysteine or the inflammatory markers CRP and plasma viscosity were detected following exercise training. Acute exercise increased neutrophil CD11b expression, but these levels were not affected by exercise training.

Conclusion: Supervised exercise training for intermittent claudication favourably modifies the fasting lipid profile and may therefore be of benefit in the secondary prevention of cardiovascular and cerebrovascular events.

Acquisition of methicillin-resistant *Staphylococcus aureus* in vascular patients

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Background: *Staphylococcus aureus* is an increasingly common cause of nosocomial infection with up to one-third of staphylococcal bacteraemias being caused by methicillin-resistant *S. aureus* (MRSA). Vascular graft infection by MRSA may result in limb loss or death. The aim of this study was to establish at which point during hospital admission MRSA is acquired.

Methods: A consecutive series of 100 patients undergoing arterial surgery were screened for MRSA carriage on admission to hospital, on exit from theatre, on discharge from the intensive therapy unit (ITU), weekly while an inpatient and on discharge from hospital. Screening was with moistened swabs from nose, throat, perineum and open wounds pooled for microbiological culture.

Results: Four patients (4 per cent) screened positive for MRSA on admission to hospital. Of the remaining 96, MRSA was identified in 16 (17 per cent) during the hospital stay: on exit from theatre (one), on exit from ITU (six) and on the ward after operation (nine). Comparing MRSA acquisition ($n = 16$) with non-acquisition ($n = 80$), the following characteristics were noted: median (range) length of stay 16 (4–66) *versus* 7 (2–50) days ($P < 0{\cdot}01$, Mann–Whitney U test); 13 of 16 *versus* 46 of 80 admitted to ITU ($P = 0{\cdot}10$, Fisher's χ^2 test); median (range) length of ITU stay 3 (1–20) *versus* 3 (1–14) days ($P = 0{\cdot}41$, Mann–Whitney U test). Frequent hospital attendance, age, emergency admission, diabetes or renal failure were not commoner in patients who acquired MRSA.

Conclusion: These data indicate that 4 per cent of patients undergoing arterial surgery are pre-existing carriers of MRSA. Acquisition of MRSA is commoner in long-stay patients (those experiencing maximum direct handling by hospital staff).

Patient satisfaction with carotid endarterectomy under general and local anaesthesia

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Background: The aim was to compare patient satisfaction for patients undergoing carotid endarterectomy (CEA) under general anaesthesia (GA) and local anaesthesia (LA) using a CEA-specific questionnaire.

Methods: Patients having CEA were randomized prospectively to LA or GA. Forty-three LA CEA procedures were compared with 42 GA CEA procedures. All patients completed a CEA experience questionnaire (CEA-EQ). The questionnaire was split into 15 preoperative and 13 postoperative questions covering aspects of the patient's level of anxiety, evaluation of information, perception of recovery and overall satisfaction. Each question was scored between 0 and 100, with a lower score indicating a 'better' experience. All item scores were treated as ordinal data. Median values are presented. Statistical analysis was performed with the Mann–Whitney U test.

Results: The two groups were matched for demographics and indications for surgery. The overall satisfaction with

CEA was high and all patients responded to the questionnaire. There was no statistically significant difference in satisfaction between patients in the GA and LA groups (705 LA, 720 GA; $P = 0{\cdot}8$). Preoperative scores (464 LA, 353 GA; $P = 0{\cdot}3$) and postoperative scores (287 LA, 248 GA; $P = 0{\cdot}9$) were similar. Levels of anxiety before operation (231 LA, 264 GA; $P = 0{\cdot}4$), evaluation of information (150 LA, 91 GA; $P = 0{\cdot}3$) and perception of recovery (99 LA, 99 GA; $P = 0{\cdot}4$) were similar for each group.

Conclusion: LA CEA was not associated with any significant increase in patient anxiety before operation or peroperative complaints. Overall patient satisfaction with CEA was extremely high and not related to anaesthetic technique.

Crescendo transient ischaemic attacks: use of preoperative transcranial Doppler-directed intravenous Dextran therapy to control symptoms and emboli before elective carotid endarterectomy

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Background: Transcranial Doppler (TCD)-directed Dextran 40 after carotid endarterectomy (CEA) has been shown to reduce early postoperative thrombosis. The efficacy of Dextran 40 at controlling symptoms and emboli before CEA was assessed in patients with crescendo transient ischaemic attacks (TIAs).

Methods: In a prospective study, patients with more than 70 per cent internal carotid artery stenosis (ICAS), with two or more symptomatic episodes within 30 days and TCD-detected emboli, were studied. Dextran 40 was commenced at $20\,\mathrm{ml\,h^{-1}}$; a repeat TCD was performed to reassess the rate of embolization. The infusion was increased in increments of $20\,\mathrm{ml\,h^{-1}}$ until symptoms and emboli were controlled. The patient then proceeded to CEA on the next elective list.

Results: Over 2 years, 19 patients were found to have more than 70 per cent ICAS with recurrent symptoms and TCD-detected emboli. The number of TIAs each patient suffered ranged from two within 10 days to four events per day. The number of emboli ranged from two to nine per h. Sixteen of the 19 patients had their emboli controlled by Dextran $20\,\mathrm{ml\,h^{-1}}$, but three required up to $100\,\mathrm{ml\,h^{-1}}$. All patients had symptoms and emboli controlled with Dextran. One patient with both unstable angina awaiting urgent coronary bypass and crescendo TIAs died from a myocardial infarction before undergoing surgery. Of the 18 patients who underwent surgery, one suffered a non-disabling postoperative stroke (which resolved fully at 6 weeks) and four patients had a wound haematoma.

Conclusion: TCD-directed Dextran 40 appears to be safe in high-risk patients before elective CEA and warrants further study.

Localized increase in matrix metalloproteinase 9 may cause rupture of abdominal aortic aneurysms

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Background: The molecular events that result in rupture of abdominal aortic aneurysms (AAAs) are unknown. Matrix metalloproteinases (MMPs) play a pivotal role in aneurysm formation and may be implicated in rupture. Two theories have been advanced to explain aneurysm rupture: a global tendency to increased proteolysis throughout the aneurysm or a localized tendency to matrix degradation at the site of rupture. The aim of the study was to define the proteolytic mechanism for aneurysm rupture.

Methods: Samples of the anterior aortic wall were obtained from 81 patients undergoing elective AAA repair ($n = 59$, median age 72 years, AAA diameter 6 cm) or emergency repair of ruptured AAA ($n = 22$, age 72 years, diameter 8·5 cm). MMP-1, MMP-2, MMP-3, MMP-9 and MMP-13, and tissue inhibitor of metalloproteinase (TIMP) 1 and TIMP-2, were extracted from the tissue and quantified by enyme-linked immunosorbent assay. In the second phase of the study, MMP levels were quantified in paired samples from the anterior sac and the site of aortic rupture obtained from nine patients with ruptured AAA.

Results: There were no significant differences in MMP and TIMP levels in the AAA sac between non-ruptured and ruptured AAAs. Analysis of paired samples from ruptured aneurysms demonstrated that the concentration of MMP-9 was seven times higher at the site of aortic rupture than in the anterior sac (98·57 (interquartile range (i.q.r.) 56·02–134·50) *versus* 13·89 (7·80–46·81) $\mathrm{ng\,mg^{-1}}$; $P = 0{\cdot}012$). The MMP-9 : TIMP-1 ratio was also significantly increased at the site of rupture (0·44 (i.q.r. 0·20–1·54) *versus* 0·12 (0·07–0·24); $P = 0{\cdot}008$).

Conclusion: These data demonstrate that aneurysm rupture may be caused by locally increased proteolytic capacity at the site of rupture. Defining the precise mechanism of aneurysm rupture may allow targeted pharmacotherapy.

Simvastatin decreases the levels of active matrix metalloproteinase 2 and the level of interleukin 6 in human aortic aneurysm explants

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Background: Inflammatory cells within the aortic wall have a pivotal role in the pathogenesis of abdominal aortic aneurysms (AAAs), through the induction of matrix metalloproteinases (MMPs) and local generation of cytokines. Simvastatin may have anti-inflammatory effects unrelated to its lipid-lowering properties, and has been proposed as a potential agent to reduce aneurysm growth. The aim of the study was to investigate the effects of simvastatin on MMP production and cytokine secretion within human aortic tissue.

Methods: Full-thickness human explants ($n = 9$) were established from aortic aneurysm wall. Explants were maintained in serum-free medium and treated with increasing doses of simvastatin (0·1–1 µmol l^{-1}) at therapeutic concentration. After 48 h in culture the tissue was harvested and prepared for histological examination and protein determination. MMPs were extracted and the activity of MMP-2 and MMP-9 was determined by gel enzymography. Tumour necrosis factor (TNF) α, interleukin (IL) 1β and IL-6 concentrations were measured in conditioned media using enzyme-linked immunosorbent assays.
Results: The level of active MMP-2 was significantly lower in explants treated with simvastatin than in the control group ($P = 0·03$, analysis of variance). There was no significant difference in active MMP-9 or in the secreted form of the enzymes. The concentration of IL-6 was decreased at the therapeutic level ($P = 0·01$, unpaired t test), although no significant difference was seen in the levels of TNF-α and IL-1β.
Conclusion: The reduction in the level of active MMP-2 suggests that simvastatin may be useful as an agent to prevent the expansion of AAAs. However, there is a complex relationship between MMP expression and cytokine levels that requires further investigation.

Perianeurysmal fibrosis is a relative contraindication to endovascular repair

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Background: Perianeurysmal fibrosis (PAF) can render open repair of inflammatory aneurysms technically difficult. Endovascular repair (EVAR) has therefore been advocated as the preferred approach for this condition. The nature of the local inflammatory response to EVAR remains unknown. If significant, such a response could exacerbate rather than ameliorate PAF. The aim of the study was to examine the incidence, course and consequences of PAF detected by computed tomography (CT) before and after EVAR.
Methods: The clinical records of patients treated by EVAR and followed for at least 6 months were reviewed. Preoperative and postoperative CT images were graded for PAF independently by three radiologists according to a standard protocol.
Results: PAF was documented before operation in six of a total of 61 patients. In two of these PAF worsened after EVAR resulting in ureteric obstruction that required ureteric stents. In the remaining four patients, PAF did not reduce after operation. PAF of low grade developed after operation in ten (18 per cent) of 55 patients with no evidence of PAF on preoperative imaging. Median follow-up was 18 (range 6–36) months. The development of periaortic fibrosis '*de novo*' after operation was statistically significant ($P = 0·002$, McNemar's test).
Conclusion: EVAR does not seem to reverse PAF if it is already present before operation and it induces this condition in approximately one-sixth of patients without evidence of preoperative PAF. The potential for this adverse inflammatory local response should be taken into account when considering EVAR for treatment of aneurysms with PAF and must be weighed against its perceived benefits.

Venous ulcer exudate inhibits *in vitro* angiogenesis

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Background: Angiogenesis is important for wound healing. Venous ulcers are sometimes slow to heal. The aim of this study was to determine whether ulcer wound exudate inhibits angiogenesis.
Methods: Acute wound fluids ($n = 7$) were collected from subcutaneous drains on the second day after operation. Venous ulcer fluids ($n = 16$) were collected by aspiration from under OpSite dressings (Smith and Nephew Medical, Hull, UK) over 4 h. All fluids were spun to remove debris, diluted to 0·5 per cent with culture medium, passed through a 0·22-µm filter and applied in triplicate to an angiogenesis kit (TCS) at days 0, 3, 6 and 9. Each 24-well plate included three wells treated with vascular endothelial growth factor (VEGF) at 2 ng ml^{-1} and three untreated controls. On day 12, the cells were fixed and stained with an antiendothelial antibody (CD31). The amount of tubule formation was quantified using image analysis based on digital photographs of five fields in each well. Tubule development was defined as the ratio of the mean tubule length in the test wells over that in the control wells for each wound fluid.
Results: Venous ulcer exudates significantly inhibited tubule development (mean 0·72 (95 per cent confidence interval 0·48 to 0·96)) compared with the effect of acute wound fluids (2·48 (0·86 to 4·10)) ($P < 0·01$) and VEGF (1·47 (1·32 to 1·61)) ($P = 0·01$). There was no difference between acute wound fluids and the stimulatory effect of VEGF.
Conclusion: Venous ulcer exudate inhibits angiogenesis, unlike acute wound fluids. This may explain why some ulcers heal slowly.

Bayesian method for comparative audit of carotid endarterectomy is superior to classical methods

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Background: Handling missing or 'noisy' data and quantifying the surgeon effect on the outcome of procedures are challenges facing comparative audit. The aim of this study was to develop a Bayesian hierarchical model that enables reliable comparison of outcome between surgeons.

Methods: Binary outcome data (death/stroke within 30 days), together with information on nine possible risk factors specific for carotid endarterectomy (CEA), were available for 1581 CEAs performed by seven vascular surgeons from four vascular units. The median age of the patients was 69 (range 37–93) years and 61 per cent were men. The data were entered into a database based on Access 97 (Microsoft, Reading, UK) and then transported to the WinBUGS (Microsoft), which uses Markov chain Monte Carlo techniques to fit complex Bayesian models. After adjusting for patient-level risk factors, the model was used compare surgeon performance. An attempt was made to rank surgeons based on the surgeon effect after risk adjustment and to identify divergent or extreme surgeons.
Results: The overall observed 30-day stroke/death rate was 4·6 per cent. The model found diabetes, stroke and contralateral internal carotid occlusion to be significant risk factors. The observed 30-day stroke/death risk varied between 1·3 and 5·2 per cent for the seven surgeons. After risk adjustment the median surgeon rank varied from 3·0 to 6·0 (95 per cent confidence interval 1·0 to 7·0). There were no divergent or extreme surgeons in the population analysed.
Conclusion: Bayesian hierarchical models handled missing and 'noisy' data and were able to quantify the surgeon effect better than classical methods. Divergent or extreme surgeons can be identified using the proposed model.

Novel magnetic resonance imaging technique to detect high-risk carotid disease: prevalence of complex plaque in patients with cerebral ischaemia

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Background: Complex atheromatous plaques are vulnerable to rupture and thromboembolism. Identification of complex carotid plaques *in vivo* could help identify patients at risk of cerebral ischaemia. The authors have previously described a novel magnetic resonance direct thrombus imaging technique (MRDTI) which demonstrates complex carotid plaque as a high signal. The carotid vessels of patients with recent cerebrovascular symptoms were imaged using MRDTI, in order to ascertain the prevalence and relevance of complex plaque.
Methods: One hundred patients undergoing assessment for carotid endarterectomy were imaged using MRDTI. The prevalence of a high signal in ipsilateral (symptomatic) and contralateral (asymptomatic) arteries was calculated.
Results: High signal was seen in 63 per cent of symptomatic vessels and 41 per cent of asymptomatic vessels ($P < 0{\cdot}01$, χ^2 test; relative risk (RR) 1·6 (confidence interval (c.i.) 1·2 to 2·1)). Moderately stenosed symptomatic vessels had at least as much high signal as their severe counterparts (80 *versus* 59 per cent; $P = 0{\cdot}07$, RR 0·8 (c.i. 0·7–1·0)).
Conclusion: This work suggests that production of cerebral ischaemic symptoms due to thromboembolism from complex carotid plaque is a particularly important mechanism in patients with symptoms occurring in the presence of more minor degrees of stenosis, many of whom are not currently offered carotid surgery. MRDTI may help to target therapy at this group.

Should all claudicants be on a statin?

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Background: The authors have investigated the implications of applying nationally accepted guidelines for the treatment of hyperlipidaemia to new outpatient referrals with suspected intermittent claudication.
Methods: A lipid profile, cardiovascular risk profile and drug history have been recorded for 425 new referrals to a vascular clinic. A total cholesterol level of more than 5 mmol l^{-1} was used as the threshold for treatment. Those with pre-existing cardiovascular disease were assumed to require secondary lipid lowering for prevention of further events. Those with no demonstrated cardiovascular disease had a 10-year coronary heart disease risk calculated using the Framingham risk equations to assess their need for primary prevention.
Results: Of 425 patients, 322 (76 per cent) were shown to have lower-limb arterial disease. Seventy-nine (19 per cent) were on a statin at presentation but 60 per cent were treated inadequately. Some 276 (80 per cent) of 346 patients not on a statin had a cholesterol level above 5 mmol l^{-1}, of whom 229 (83 per cent) merited treatment. Overall, 65 per cent of all patients referred, 85 per cent of those with a cholesterol level greater than 5 mmol l^{-1} and 76 per cent of those with true intermittent claudication had an indication for lipid-lowering therapy.
Conclusion: The majority of patients with intermittent claudication require lipid-lowering therapy and those attending a vascular clinic and subsequently shown not to have arterial disease represent a subgroup at greater than normal risk. It is unlikely that a prospective trial of lipid-lowering therapy could be undertaken for peripheral arterial disease because the majority of patients have a pre-existing condition that would exclude them from a trial.

Composite sequential grafts for femorocrural bypass

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Background: In order to review the efficacy of a modification of the composite sequential femorocrural bypass graft adopted in 1985, a retrospective case-note review was undertaken. The grafts combined a prosthetic femoropopliteal section with a popliteal-to-crural section using autologous vein, linked via a common intermediate anastomosis sited on the above-knee popliteal artery.

Methods: Between 1985 and 2000, 68 grafts of this type were constructed in 65 patients who were suffering from critical leg ischaemia and who had insufficient long saphenous vein to construct a single-stage bypass. Thirty-three (49 per cent) of these operations were performed following failure of a previous graft. In 22 limbs (32 per cent), angiography had demonstrated no patent segment of the above-knee popliteal artery and in these cases a local popliteal endarterectomy was performed to restore a lumen to receive the composite anastomosis and to provide additional outflow. Distal anastomoses were to the anterior tibial (17), posterior tibial (14), peroneal (26), dorsalis pedis (three) and plantar (three) arteries and tibioperoneal trunk (two).

Results: The 2-year cumulative primary patency, secondary patency and limb salvage rates were 66, 72 and 74 per cent respectively. Localized popliteal endarterectomy did not compromise graft patency ($P = 0{\cdot}15$, log rank test). The 30-day mortality rate for the series was 8 per cent.

Conclusion: In the absence of sufficient autologous vein, patients requiring bypass to crural arteries can be offered reconstruction by means of composite sequential grafting with comparable results. Furthermore, a non-patent popliteal segment is not a contraindication for composite sequential bypass reconstruction.

Influence of mode of presentation on infrainguinal bypass graft patency and limb salvage rates in critical leg ischaemia

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Background: Critical leg ischaemia (CLI) is often classified as a tissue necrosis presentation, which includes gangrene or tissue loss (ulcer) presentation or rest pain alone. The management outcome for the three groups, and especially for those with gangrene and tissue loss, is often considered together despite the different nature of the conditions. The aim was to determine the effects of the mode of presentation (gangrene, tissue loss or rest pain) of CLI on graft patency and limb salvage rates.

Methods: Some 152 infrainguinal bypass grafts performed in 128 patients for CLI between 1994 and 1999 were studied. Grafts were classified according to the mode of presentation (gangrene, tissue loss or rest pain). Grafts were followed by regular clinical and duplex examinations. Mean follow-up was 29 (range 12–60) months.

Results: Patient demographics, risk factors and percentage of crural and prosthetic grafts were not statistically different between the three groups. Five-year cumulative primary patency (46, 70 and 72 per cent for gangrene, tissue loss and rest pain groups respectively; $P = 0{\cdot}01$), secondary patency (48, 76 and 75 per cent; $P < 0{\cdot}01$) and limb salvage (59, 87 and 83 per cent; $P = 0{\cdot}01$) rates were significantly worse for the gangrene group than for the tissue loss and rest pain groups.

Conclusion: Gangrene is a distinct subcategory of CLI with a worse prognosis than tissue loss and rest pain, and should not be classified with tissue loss as a tissue necrosis presentation.

Prospective study of the Distaflo graft

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Background: The rationale behind the Distaflo graft (Bard Impra, Murray Hill, New Jersey, USA) is inhibition of myointimal hyperplasia through optimization of haemodynamics at the distal anastomosis. This study reports the early clinical results.

Methods: Patients with critical ischaemia, but no autologous vein, underwent infrainguinal bypass using a Distaflo graft. Approved protocols, incorporating clinical and duplex assessment, provided prospective patient and clinical data. A blinded, retrospective control group of Miller cuff grafts was selected, matching age, gender, diabetes and limb necrosis. One-year cumulative patency, limb salvage and survival rates were calculated using Kaplan–Meier analysis. Log rank test enabled comparison between groups.

Results: Fifty Distaflo grafts were inserted over 29 months into 46 patients (median age 68·5 (range 40–90) years; 27 men), of which 27 (54 per cent) were repeat procedures. Proximal anastomoses were to common femoral arteries in 40 cases (80 per cent); distal anastomoses were to popliteal vessels in 20 cases (40 per cent) and tibial vessels in 30 cases (60 per cent). Mean follow-up was 394 days, with 1-year cumulative patency, limb salvage and survival rates of 39, 50 and 82 per cent respectively. The Miller cuff control group had a mean follow-up of 435 days, with rates of 49, 56 and 85 per cent respectively. Log rank comparisons between the two groups showed no significant differences ($P = 0{\cdot}23$, $P = 0{\cdot}41$ and $P = 0{\cdot}74$ respectively).

Conclusion: The Distaflo graft has 1-year patency, limb salvage and survival rates similar to those of the Miller cuff, justifying its use as an alternative in distal prosthetic arterial reconstruction for critical limb ischaemia.

Ischaemic rest pain relief improved with intravenous ketamine: randomized trial

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Background: Ketamine has for some years been used successfully as an adjunct to neuropathic pain control in patients with cancer. Ischaemic rest pain has similar clinical symptoms; therefore a randomized controlled trial was set up to investigate the efficacy of ketamine in ischaemic rest pain.

Methods: This was a prospective double-blind randomized controlled trial. Patients initially had their analgesic regimen titrated to pain requirements using regular morphine. They subsequently received a single intravenous infusion of either ketamine 0·6 mg kg^{-1} in 500 ml saline or placebo (500 ml normal saline) over 4 h. The principal pain measurement taken was the Brief Pain Inventory which was administered at four separate intervals during the study.
Results: Thirty-five patients with poorly controlled rest pain completed the study. The percentage pain relief that the patients attributed to their medication rose significantly in the group receiving ketamine from 50 per cent immediately before infusion to 65 per cent 24 h after infusion and 69 per cent 5 days after infusion. During the same interval the placebo group fell from 58 to 56 per cent pain relief 24 h after infusion and then to 50 per cent relief 5 days later. This was a statistically significant difference ($P < 0·05$ from preinfusion to 24 h after infusion, and $P = 0·01$ from preinfusion to 5 days after infusion; two-tailed t-test). The ketamine group also showed a significant improvement in average pain scores, general activity and enjoyment of life.
Conclusion: A single infusion of intravenous ketamine in combination with regular opioid analgesia improved pain relief in patients with rest pain. Improved pain control may delay or occasionally avoid amputation.

Therapeutic, economic and logistical implications of thrombin injection in iatrogenic femoral artery false aneurysms

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Background: Treatment of iatrogenic femoral artery false aneurysms (IFFAs) has been revolutionized by the introduction of endoluminal ultrasound-guided thrombin injection. This study evaluated the therapeutic, economic and logistical implications of thrombin injection in the management of these aneurysms compared with the standard surgical approach.
Methods: Since 1996, 75 IFFAs that failed conservative treatment were referred to this unit. All aneurysms between 1996 and 1997 ($n = 20$) were managed surgically. In 1998–1999 the feasibility of thrombin injection was evaluated in all aneurysms ($n = 28$), with three failing the indication criteria. Since 2000 all aneurysms ($n = 26$), except one with femoral neuropathy, were injected.
Results: Surgically treated aneurysms ($n = 24$) measured 2·0–8·1 (median 4·2) cm in maximal diameter, were mainly solitary (83 per cent), due to right-sided (75 per cent) common femoral (79 per cent) puncture, preceding repair by 1–38 (median 5) days. Operating time was 30–165 (median 65) min, stay in the high-dependency unit (HDU) was 1–11 (median 2) days and hospital stay was 2–30 (median 6) days. Opiate analgesia was required for 1–4 days and antibiotics were given for 1–30 (median 3) days. Complications included wound infection (47 per cent), seroma (12 per cent) and dehiscence (8 per cent). Aneurysms treated with thrombin ($n = 51$) measured 1·8–9·6 (median 3·9) cm in maximal diameter (P not significant), were mainly solitary (80 per cent) (P not significant), due to right-sided (82 per cent) (P not significant) common femoral (82 per cent) (P not significant) puncture, preceding injection by 1–29 (median 4·5) days (P not significant); hospital stay was less than 24 h, early recurrence ($n = 2$) was treated with repeat thrombin injection and recovery was uneventful.
Conclusion: Thrombin injection is an effective, low-complication and low-cost (£250 per aneurysm) treatment for IFFA, enabling discharge within 24 h. Further to anaesthetic risk and invasiveness, standard surgical management is expensive (more than £2500 per aneurysm), requires a stay in the HDU and longer hospital stay, with a complication rate exceeding 60 per cent.

Cost analysis of haemodilution and cell salvage in elective aortic reconstruction

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Background: Autologous blood transfusion reduces homologous blood requirements in elective aortic surgery but the cost-effectiveness of this approach remains unproven. The costs of autologous *versus* homologous transfusion in aortic surgery were evaluated in a prospective multicentre randomized trial.
Methods: One hundred and forty-five patients were randomized to either standard transfusion practice (homologous) or a combination of acute normovolaemic haemodilution and intraoperative cell salvage (autologous). Costs for each inpatient admission were identified. Cell salvage costs were assigned on the assumption of a base activity of 50 cases per annum and the provision of a dedicated cell salvage operator. Differences were determined by bias-corrected bootstrap analysis.
Results: Two hundred and fifty-one homologous units were transfused in 'homologous' and 103 in 'autologous' operations ($P = 0·008$). There was no difference in morbidity and mortality rates, and hospital stay. There was no significant difference in the mean cost of a treatment episode: £5859 for 'homologous' and £5404 for 'autologous' (mean difference −£455 (95 per cent confidence interval (c.i.) −£2231 to £1342)). Transfusion-related mean costs accounted for only 6 per cent of the total expenditure in 'homologous' (£341) and 7 per cent in 'autologous' (£357) procedures, with a mean difference of £17 (95 per cent c.i. −£184 to £174). Two-way sensitivity analysis of transfusion costs in isolation confirmed cost neutrality with autologous transfusion for an activity of 20 cases per annum with a cell salvage operator

(mean difference £151 (95 per cent c.i. −£19 to £322)) or for an activity of 150 cases per annum without a cell salvage operator (mean difference −£84 (95 per cent c.i. −£260 to £92)).

Conclusion: Autologous transfusion in aortic surgery is cost neutral even when surgical activity is low.

Elective abdominal aortic aneurysm surgery on a group and save alone

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Background: In the light of concerns over homologous blood, surgeons have reduced their use of transfusion. 'Rapid spin' cross-matching can provide blood on demand in 15–20 min. The efficacy and safety of a group and save policy has been evaluated prospectively in a consecutive series of abdominal aortic aneurysm (AAA) repairs.

Methods: Patients with a haemoglobin level greater than 12 g dl^{-1} were grouped and screened for abnormal antibodies. Those with a haemoglobin level of less than 12 g dl^{-1} had 2 units of blood cross-matched. Cell salvage was available and acute normovolaemic haemodilution was employed according to a concurrent protocol. Clinical and transfusion data were collected prospectively and validated against transfusion records.

Results: Between January 1999 and 2001, 72 patients were studied. Fifty had a group and save, and 22 were cross-matched for clinical reasons, at the request of a different anaesthetist or in error. Some 55 per cent of patients received no blood transfusion. Mean intraoperative transfusion was 0·1 units of homologous blood, 0·6 units of ANH and 0·8 units of salvaged blood. No problems were encountered with the availability of blood. Complications were similar in the two groups. Perioperative blood utilization was greatly increased; 72 per cent of units requested were transfused in grouped patients compared with 38 per cent in cross-matched patients.

Conclusion: AAA surgery requires minimal banked blood if autologous techniques are available; routine cross-matching is not mandatory in the majority of cases and should blood be required it may be provided quickly and safely on demand. Using this protocol the efficiency of blood transfusion in elective AAA surgery is much improved.

Minimally invasive incision for abdominal aortic aneurysm repair

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Background: The aim was to evaluate the feasibility of a minimally invasive incision for the treatment of patients with abdominal aortic aneurysm (AAA).

Methods: The study was a comparison of 16 patients undergoing elective AAA repair (seven minimally invasive and nine conventional repairs). Patients in the minimally invasive group had a 10–12-cm midline incision whereas those in the conventional group had a long midline incision. The groups were comparable in terms of preoperative morbidity, age and gender. Outcome measures analysed were C-reactive protein (CRP) concentration on the first postoperative day, length of operation, blood loss, duration of postoperative epidural, return of gastrointestinal function and length of hospital stay.

Results: There was one bifurcated graft in the minimally invasive group compared with two in the conventional group. The mean size of aneurysm was 6·1 and 6·4 cm (P not significant) and mean length of the incision was 12·1 and 28·5 cm ($P = 0·04$) for minimally invasive and conventional operations respectively. Mean CRP level was 68·4 *versus* 84·1 ($P = 0·07$). Length of operation was 111 compared with 145 min ($P = 0·03$) and blood loss was 700 *versus* 1200 ml (P not significant). The duration of postoperative epidural was 2 *versus* 4 days ($P < 0·01$). Return of gastrointestinal function took 2·5 *versus* 4·3 days (P not significant). Hospital stay was 11·6 *versus* 14·7 days (P not significant).

Conclusion: Elective repair of AAA through a small incision is feasible and seems to have a beneficial effect compared with the traditional repair. A large randomized trial should be undertaken to confirm these findings.

Fate of the proximal aortic neck following endovascular aortic repair

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Background: Endovascular aortic repair (EVAR) depends on a stable fixation at the proximal neck of the aneurysm to result in a durable repair. The aim of this study was to determine whether the infrarenal proximal aortic neck continues to expand following EVAR.

Methods: EVAR was performed in 151 patients between December 1995 and June 2001. Follow-up was done according to the EUROSTAR criteria with contrast-enhanced computed tomography and measurement of the proximal aortic neck at a level distal to the renal arteries.

Results: Of the 151 patients, 30 had completed follow-up to 36 months. In these patients, the mean(s.d.) preoperative proximal neck diameter was 21·6(1·8) mm. At 6 months, the mean proximal neck diameter was 22·6(2·5) mm ($P = 0·02$). At 36 months the mean neck diameter had increased by a further 1·4 mm (mean diameter 24·0(2·5) mm) from the 6-month measurement ($P = 0·01$). There have been six graft migrations among the 151 patients with a median onset of 30 (range 12–48) months. The mean increase in proximal neck diameter before graft migration was 4·8(3·1) mm.

Conclusion: Within the first 6 months following EVAR there appears to be a relatively rapid increase in the proximal neck diameter. This increase continues but at a slower rate of 0·6 mm per year. This expansion is ongoing and raises the question of the stability of the proximal neck fixation. This may bring into doubt the long-term durability of devices that are fixed in the infrarenal aortic segment.

Four and a half decades of ruptured abdominal aortic aneurysm repair: a meta-analysis

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Background: Ruptured abdominal aortic aneurysm (RAAA) accounts for approximately 9000 deaths per annum in England and Wales and this figure has been steadily increasing over the past two decades. Operative repair of RAAA is associated with a high mortality rate but reported figures vary widely. The aim of this study was to estimate the operative mortality rate of RAAA repair, to quantify how this has changed over time and to examine changes in the demographics of patients undergoing RAAA repair.
Methods: A meta-analysis of all English language literature describing the outcome of RAAA repair was performed. Articles were rejected if RAAA was not defined explicitly as blood outside the aortic wall on laparotomy. Standard random-effects meta-analysis was applied to determine the overall mortality rate and meta-regression analysis was used to determine changes over time.
Results: Some 171 papers were included in the analysis giving details of 21 523 patients over 43 years (1954–1997). The overall mortality rate was 48·2 (95 per cent confidence interval 46·3 to 50·1) per cent. Meta-regression analysis of mortality demonstrated a constant reduction of approximately 4·9 per cent per decade. The intraoperative mortality rate has remained constant over time. Both the mean age and the number of female patients undergoing surgery have increased over time. Papers reporting higher proportions of female patients were associated with high intraoperative mortality rates but not high overall mortality rates.
Conclusion: The mortality rate following RAAA repair remains high but has gradually decreased over the past four decades. The failure to improve the mortality rate may be explained by increasing numbers of high-risk patients undergoing surgery.

Implications of intensive care bed non-availability and the centralization of vascular services in the treatment of ruptured abdominal aortic aneurysm

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Background: The centralization of vascular services and the non-availability of a bed in the intensive therapy unit (ITU) or of a vascular surgeon may necessitate patient transfer, delaying operation for ruptured abdominal aortic aneurysm (RAAA) with adverse consequences for the patient.
Methods: This study was a postal survey of 169 vascular units.
Results: The response rate was 76 per cent with 126 replies for analysis. Over 40 per cent of institutions have no formal vascular on-call rota. Surgeons with no vascular interest operate on RAAAs in over half of all institutions without an on-call rota. Nearly 50 per cent of institutions without an on-call rota transfer patients with a RAAA before operation. Where no ITU bed is available only 5 per cent of institutions transfer patients before surgery. Nearly 90 per cent operate and then transfer or ventilate in theatre. A quarter of all teaching/tertiary referral centres decline tertiary referrals if no ITU bed is available. Only 10 per cent of institutions have a predetermined policy in the event of non-availability of a bed in the ITU.
Conclusion: There is considerable evidence supporting the centralization of vascular services, although centralization means that in 30 of 126 centres surveyed RAAAs are repaired by surgeons without a vascular interest. Institutions are far more likely to transfer, however, (and hence delay) when no surgeon is available than when there is no ITU bed. This survey confirms inadequate ITU bed provision in most institutions; few units have a policy in place for the management of RAAA where no bed is available and, not surprisingly, many units report strained relations between surgeons, anaesthetists and managers.

POSSUM-based models accurately predict mortality for aortic aneurysm repair

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Background: Models based on the Physiological and Operative Severity Score for enUmeration of Mortality and morbidity (POSSUM) scoring system have been advocated as possible tools for comparative audit for abdominal aortic aneurysm (AAA) repair. The aim of this study was to test the predictive accuracy of POSSUM, P-POSSUM, P-POSSUM (physiology only; PS), V-POSSUM and V-POSSUM (PS) models for various modes of presentation of AAA.
Methods: Some 470 AAAs (297 elective, 70 urgent, 32 stable ruptured and 71 ruptured shocked) performed by five vascular surgeons from 1992 to 2000 were analysed. The mean age of the patients was 72 (range 43–87) years and 83 per cent were men. The physiological and operative variables and the 30-day mortality data were collected on preprinted sheets and entered on to a database. Predicted mortality was calculated using equations described by the relevant authors. The predictive accuracy of the model was analysed using χ^2 analysis.
Results: The observed 30-day mortality rates for elective, urgent, stable ruptured and ruptured shocked aneurysms were 6 per cent (18 of 297), 10 per cent (seven of 70), 25 per

cent (eight of 32) and 21 per cent (15 of 71). The P-POSSUM, V-POSSUM and V-POSSUM (PS) models had a better predictive accuracy for elective and urgent categories ($P > 0{\cdot}15$, $\chi^2 < 9{\cdot}0$). The V-POSSUM (PS) model accurately predicted mortality rate for the ruptured stable category ($P = 0{\cdot}6$, $\chi^2 = 2{\cdot}9$), while none of the models accurately predicted mortality rate for the ruptured shocked AAAs ($P < 0{\cdot}05$).

Conclusion: The V-POSSUM (PS) model accurately predicted mortality rate for elective, urgent and ruptured stable AAAs while P-POSSUM and V-POSSUM models were accurate only for elective and urgent AAAs.

Stent grafts significantly reduce mortality and morbidity of thoracic aortic disease compared with open surgery

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Background: Thoracic stent grafts were introduced to treat aortic pathology in 1992. Initially the devices were home made but commercially made stent grafts are now available. A recent multicentre audit of the results of thoracic aortic aneurysm repair showed a mortality rate of 28 per cent. The results of open surgery were compared with those of stent grafts for all patients with thoracic aortic disease presenting to a single centre.

Methods: Data were kept prospectively on 108 patients undergoing thoracoabdominal intervention between 1992 and 2001.

Results: Thirty-six patients underwent elective open repair with a mortality rate of 27 per cent compared with 24 patients undergoing stent graft repair with no deaths. Twenty-eight patients underwent urgent open repair with a mortality rate of 54 per cent compared with 20 patients undergoing urgent stent graft repair with a mortality rate of 15 per cent.

Conclusion: Although it is difficult to compare open repair with endoluminal repair for thoracic aortic pathology, the benefits of stent grafts are clear. Endoluminal repair is associated with a significantly lower mortality rate, and the incidence of cardiorespiratory, renal, visceral and neurological complications is much lower. In centres with suitable experience this technique offers important advantages but does not preclude open surgery.

Technical changes in the treatment of type B dissections are associated with better outcome

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Background: Treatment of type B aortic dissection is primarily with hypotensive therapy unless there is evidence of rupture, end-organ ischaemia or continuing pain, when surgery is indicated. Approximately one-third of patients will subsequently develop aneurysms that require intervention.

Methods: A consecutive series of patients was assessed. Traditional 'clamp and go' surgery was used in the first half of the series. This was compared with techniques introduced later, which included partial cardiopulmonary bypass, drainage of cerebrospinal fluid, and selective visceral perfusion and cooling. Endoluminal repair was also available for some of the later patients.

Results: Seventeen patients were treated. Two of ten elective patients, one of two treated as an emergency and one of five treated urgently died. Of nine patients treated surgically two developed paraplegia and three died. Causes of death included myocardial infarction, coagulopathy and failure to control a ruptured aneurysm. Only one patient of eight treated with a stent graft died, from pulmonary embolus. No patient had developed paraplegia because visceral perfusion and partial cardiopulmonary bypass allowed the unhurried attachment of intercostal arteries.

Conclusion: The use of selective visceral perfusion and cooling, partial cardiopulmonary bypass and cerebrospinal fluid drainage decreased the incidence of death and paraplegia in surgical patients. Endoluminal repair with stent grafts potentially offers a major improvement in the treatment of patients with type B dissection and is associated with minimal morbidity and mortality rates. Long-term follow-up is essential.

No short cuts for aneurysm screening

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Background: Screening of 65-year-old men in Gloucestershire for abdominal aortic aneurysms currently involves approximately 2300 new ultrasound scans yearly for the county's 520 000 population. The authors investigated possibly reducing the number of scans necessary by inviting only higher-risk patients, selected either by a prescreening questionnaire or from information held by general practitioners (GPs).

Methods: Some 1448 consecutive 65-year-old men attending for aneurysm screening completed a questionnaire on their smoking habits and history of hypertension. GPs were asked for the information available on each patient's smoking and blood pressure history. Various risk factors were identified (smokers, ex-smokers, hypertensives, etc.) and aortic measurements were analysed to examine the effect on detection sensitivity for either enlarged aortas (more than 2·5 cm in diameter) or aneurysms (over 3·9 cm in diameter) of screening groups of patients defined by different combinations of these criteria.

Results: The prevalence of both enlarged aortas and aortic aneurysms was, not surprisingly, significantly higher in smokers and in patients with hypertension, although significant numbers were detected in patients with neither of these risk factors. As a result, it was not possible to define a high-risk population for screening that produced a worthwhile reduction in numbers screened without an unacceptable fall in detection sensitivity. For example, excluding normotensive patients who had stopped smoking for over 10 years reduced screening numbers by 27 per cent but resulted in failure to detect 19 per cent of aneurysms. Data held on GP computer systems correlated poorly with information available from the patients.
Conclusion: Non-selective screening of all 65-year-old men remains the method of choice for aneurysm detection.

Carotid artery disease and stroke during coronary artery bypass surgery: a critical review of the literature

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Background: Vascular surgeons are increasingly asked to advise on the management of coexistent carotid and cardiac disease, particularly regarding the appropriateness of staged or synchronous carotid endarterectomy (CEA). No randomized trials are available and no systematic reviews have been performed.
Methods: This was a systematic review of the causes of stroke following coronary artery bypass grafting (CABG) with specific reference to the role of carotid artery disease.
Results: The risk of stroke after CABG was 2 per cent. Two-thirds occurred after day 1 and 23 per cent of those affected died. Some 91 per cent of screened CABG patients had no significant carotid artery disease and had an incidence of stroke after CABG of less than 2 per cent. The stroke risk increased to 3 per cent in predominantly asymptomatic patients with a unilateral 50–99 per cent stenosis, 5 per cent in those with bilateral 50–99 per cent stenoses and 7–11 per cent in those with occlusion. Significant predictive factors for stroke were: (1) carotid bruit (odds ratio (OR) 3·6 (95 per cent confidence interval 2·8 to 4·6)), (2) previous stroke or transient ischaemic attack (OR 3·6 (2·7 to 4·9)) and (3) severe carotid stenosis or occlusion (OR 4·3 (3·2 to 5·7)). However, the review indicated that 50 per cent of stroke sufferers did not have significant carotid disease and 60 per cent of infarctions on computed tomography could not be attributed to carotid disease alone.
Conclusion: Carotid disease is an important aetiological factor in the pathophysiology of stroke after CABG. However, even assuming that prophylactic CEA carried no risk, it could only ever prevent about 40 per cent of procedural strokes.

Effect of best medical treatment on carotid stenosis in patients with diabetes from the Asymptomatic Carotid Surgery Trial

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Background: The Asymptomatic Carotid Surgery Trial (ACST) is seeking to establish the role of carotid endarterectomy (CEA) in asymptomatic carotid stenosis. Some 19 per cent of patients in the ACST are diabetic. On entry patients receive best medical treatment (BMT) and half undergo CEA. BMT includes the use of lipid-lowering treatment (LLT), which has increased since the trial began in 1993. It has been shown that LLT can reduce carotid intimal medial thickness. The changes in carotid stenosis in those on BMT were investigated over 4 years.
Methods: Collaborating physicians were given information at the start of the study advising on current BMT to prevent stroke. Patients underwent duplex scanning of the carotid arteries on entry, at 4 months following randomization and then annually thereafter. A total of 219 patients with complete data sets for 4 years were studied (17 per cent diabetic, $n = 37$). All remained asymptomatic and did not undergo CEA.
Results: Mean(s.d.) percentage carotid stenosis in the whole group did not increase; it was 76·8(10·8) per cent at baseline and 76·7(13·3) per cent at 4 years, a decrease of 0·1 (s.e. 0·8) per cent. However, stenosis in diabetic patients increased by 3·4 (95 per cent confidence interval (c.i.) 0·4 to 6·3) per cent while in non-diabetic patients it regressed by 0·8 (95 per cent c.i. −2·5 to 0·8) per cent ($P = 0{\cdot}036$).
Conclusion: In patients who remained asymptomatic carotid stenosis did not progress. In diabetic patients mean stenosis did increase over 4 years despite BMT. The longer-term effects of BMT should be clear when the ACST is completed.

Reoperation for neurological complications following carotid endarterectomy

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Background: The place of surgical re-exploration after carotid surgery when neurological complications occur is poorly defined. This study investigated the indications for, and outcomes following, carotid artery re-exploration at a single centre.
Methods: Patients suffering neurological events within 30 days of carotid endarterectomy were identified from a computerized database. Case notes were interrogated for time to onset of symptoms, use of carotid artery imaging and patients undergoing re-exploration. Reoperation findings, operative procedure and clinical outcome at 30 days were determined.

Results: Between September 1984 and November 2000, 780 carotid endarterectomies were performed with an incidence of major stroke or death of 2 per cent. Twenty-five of 51 patients who experienced transient or permanent neurological events following surgery returned to theatre. Re-exploration was more common for early postoperative events (1–24 h), with 70 per cent of cases re-explored, compared with 25 per cent of patients with perioperative events (less than 1 h) and 29 per cent with late postoperative events (more than 24 h) ($P = 0{\cdot}02$, χ^2 test). Carotid artery thrombosis was found in 43 per cent of re-explorations, a flap or other technical cause in 14 per cent and nothing abnormal was found in 43 per cent. No significant difference in mortality rate, or major or minor functional deficits at 30 days, was found for patients whose carotids were and were not re-explored ($P = 0{\cdot}45$, χ^2 test).

Conclusion: Half of patients experiencing neurological complications following carotid endarterectomy underwent re-exploration, and a cause was identified and secondary procedure undertaken in 57 per cent. It was not possible to detect a significant improvement in early clinical outcome for carotid artery re-exploration compared with conservative management.

Intra-abdominal pressure and cytokine release following surgery for abdominal aortic aneurysm

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Background: Raised intra-abdominal pressure (IAP) causes decreased venous return, raised intrathoracic pressures, and renal and visceral dysfunction. Raised IAP may play a significant role in the development of systemic inflammation and multiple organ failure following repair of ruptured abdominal aortic aneurysm (AAA). The study aimed primarily to determine the relationship between IAP and systemic cytokine generation following AAA repair. The effect of IAP on cardiovascular, respiratory, renal and metabolic function was also assessed.

Methods: IAP, cytokine production (interleukin (IL) 6, tumour necrosis factor (TNF) α), and cardiovascular, respiratory and renal function were quantified in 46 patients undergoing repair of an AAA (30 elective, one death; 16 ruptured, six deaths). Measurements were made at the end of surgery and 24 h later. Values are presented as median (interquartile range); analysis used non-parametric statistics.

Results: IAP was raised in patients undergoing repair of ruptured AAA compared with elective surgery (16·5 (13–22·5) *versus* 11 (9–14) mmHg; $P < 0{\cdot}01$). Similarly, IAP (16 (16·5–22·5) *versus* 13·5 (10–18) mmHg; $P = 0{\cdot}01$), and levels of IL-6 (446 (164–1061) *versus* 98 (73–155) pg ml^{-1}; $P < 0{\cdot}01$) and TNF-α (3·7 (3·2–6·9) *versus* 2·3 (1·7–3·2) pg ml^{-1}; $P < 0{\cdot}01$) were significantly higher in patients who died after operation. The level of IAP correlated with both IL-6 (r^2 31·5 per cent, $P < 0{\cdot}01$) and TNF-α (r^2 34·9 per cent, $P < 0{\cdot}01$) concentrations. IAP also correlated with urine output ($P = 0{\cdot}02$), base excess ($P = 0{\cdot}01$), oxygen saturation ($P = 0{\cdot}03$) and right atrial filling pressure ($P = 0{\cdot}02$).

Conclusion: These data show a strong relationship between IAP and cytokine generation following aneurysm surgery. Management of IAP after AAA repair may potentially reduce the incidence and severity of systemic inflammation and organ dysfunction.

Mid-term results of the RETA registry

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Background: The Registry for Endovascular Treatment of abdominal aortic Aneurysms commenced in 1996. One thousand patients were registered before the commencement of the endovascular aneurysm repair trial in 2000.

Methods: The mid-term outcome of the 1000-patient cohort was analysed. Outcome data were returned for the following number of patients: 728 at 1 year (81 per cent follow-up), 372 at 2 years (73 per cent follow-up), 161 at 3 years (74 per cent follow-up) and 65 at 4 years (76 per cent follow-up).

Results: The mortality rates were 12, 10, 8 and 8 per cent at 1, 2, 3 and 4 years respectively. The majority of deaths were unrelated to the endovascular repair. However, ruptures did occur, with six (1 per cent) reported in the first year and four (1 per cent) in the second. Three of these patients were known to have a persistent proximal endoleak. Complications related to the device or aneurysm occurred in 12, 15, 14 and 20 per cent of patients at 1, 2, 3 and 4 years respectively. The commonest problem was a secondary endoleak, followed by graft kink or occlusion. Further endovascular treatment was successful for most of these.

Conclusion: Most mid-term deaths following endovascular repair are due to unrelated co-morbidity. Persistent proximal endoleaks carry a high risk of rupture. Complications related to the device or aneurysm occur at a constant rate of about 10 per cent per year. The continued surveillance and further endovascular interventions required increase the cost of the procedure.

Five-year survival after open *versus* endovascular abdominal aortic aneurysm repair

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Background: There are few data regarding the long-term outcome of stent graft repair for abdominal aortic aneurysm (AAA). To determine cumulative survival rates, this study compared the 5-year follow-up after endovascular aortic aneurysm repair (EVAR) with that of open repair (OR).

Methods: All patients undergoing elective AAA repair during a 2-year interval (1996–1997) were studied. Patients were selected for EVAR on anatomical criteria alone. Patients unsuitable for EVAR underwent OR using a standard inlay technique. All patients were followed according to EUROSTAR criteria. Survival and intervention-free survival rates were assessed using Kaplan–Meier survival curves.

Results: A total of 115 patients was studied (OR 69, EVAR 46). The median age for the two groups was similar (OR 72 (range 54–86) years, EVAR 71 (range 45–88) years; *P* not significant). Median follow-up was 47 (range 14–66) months. There was no significant difference in survival either at 30 days (88 per cent for OR *versus* 93 per cent for EVAR) or at 5 years (73 *versus* 67 per cent respectively). However, intervention-free survival rate was significantly higher for OR (97 *versus* 42 per cent; $P < 0.001$).

Conclusion: Patients selected for EVAR have no 5-year survival advantage over those undergoing OR of an AAA. In fact, this group has a significantly increased risk of requiring reintervention in order to maintain stent graft integrity. Until the EVAR trials report, these findings will have significant implications when counselling patients on the relative merits of aortic stent grafting compared with OR.

Outcome of endovascular abdominal aortic aneurysm repair in high-risk patients

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Background: Concerns about the long-term durability of endovascular aortic aneurysm repair (EVAR) have resulted in a tendency for clinicians to reserve this procedure for higher-risk patients with a limited life expectancy. The study was undertaken to assess the validity of this strategy.

Methods: The database of a large multicentre registry of EVAR procedures was interrogated to identify patients deemed 'unfit for open repair'. Outcomes were compared with those of patients who were considered fit for open surgery. Additionally, the medium-term survival of 'unfit' patients after EVAR was compared with a theoretical comparable cohort of patients with untreated aortic aneurysms (rupture rates derived from published reports) in a mathematical model.

Results: Of a total of 3075 patients registered, 399 were considered unfit to undergo open surgery (group 1), 151 were unfit for general anaesthesia (group 2) and 2525 were at 'normal' risk (group 3). Early and late mortality rates were higher in the unfit categories (groups 1 and 2). Life-table analysis demonstrated a 3-year survival rate in unfit patients of 68 per cent compared with 83 per cent for those of 'normal' operative risk ($P < 0.01$). Patients in groups 1 and 2 with aneurysms of less than 6·0 cm and more than 6·0 cm had a 2-year survival rate of 80 and 68 per cent respectively ($P = 0.02$). The mathematical model indicated that EVAR in unfit patients reduced the mortality rate at 3 years by 18 per cent compared with that in a cohort of patients with untreated aneurysms. There was a similar advantage associated with EVAR for unfit patients with small (less than 6·0 cm) aneurysms and larger aneurysms.

Conclusion: Until the results of clinical trials are known, EVAR is a justifiable option for unfit patients.

Prospective multicentre study of the natural history of atherosclerotic renal artery stenosis

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Background: There is a high incidence of renal artery stenosis with concurrent vascular disease. Intervention to avoid dependence on dialysis has been advocated. Few studies have characterized the natural history of the condition.

Methods: Some 98 subjects (71 men) with significant, more than 50 per cent, atherosclerotic renal artery stenosis (unilateral 64, bilateral 34) were recruited prospectively. Measurements of creatinine concentration, diastolic blood pressure and renal size were recorded at baseline and at 6-monthly intervals. Renal artery intervention was undertaken at the discretion of the managing clinician.

Results: Complete data were available for 85 patients with a minimum follow-up of 2 (mean 2·5) years. The mean age was 71 years. All 52 patients with unilateral disease were managed conservatively (group 1); 12 of the 33 patients with bilateral disease had intervention (group 2) and 21 had no intervention (group 3). The overall mortality rate was 32 per cent at 2 years and was similar in all three groups. Only three deaths were directly related to renovascular disease (coronary disease accounted for the majority of other deaths). All three patients requiring dialysis died within 1 year. In survivors in groups 1 and 2 there was a significant increase in creatinine concentration at follow-up, but not in group 3 ($P < 0.01$ and $P = 0.04$ respectively, Wilcoxon signed rank test for paired observations). Median blood pressure did not increase significantly at follow-up.

Conclusion: Renal artery stenosis (both unilateral and bilateral) had a poor prognosis, which was not directly attributable to renal failure. Intervention for bilateral disease did not prevent deterioration in renal function.

Long-term outcome of surgical revascularization for bilateral renal artery stenosis

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Background: Patients with bilateral renal artery stenosis (BRAS) have a high annual mortality rate (20–30 per cent) and comprise 15–20 per cent of the chronic dialysis population; 40 per cent of stenoses greater than 75 per cent occlude within 1 year. This paper reports the long-term outcome of surgery for BRAS.

Methods: Thirty patients (age 52–79 years, 15 men and 15 women) with more than 70 per cent BRAS who underwent surgery between 1990 and 1998 were reviewed (notes, general practitioner, Register of Deaths). Before operation 22 of 30 had a single functioning kidney and eight had potentially correctable BRAS. Indications for surgery were renal salvage (26) or intractable hypertension (four). Median creatinine concentration was 191 (range 104–520) μmol l^{-1}. Eighteen patients required aortic reconstruction (11 abdominal aortic aneurysm, seven chronic ischaemia; two tube and 16 bifurcated grafts) and 12 underwent renal revascularization alone. Saphenous vein grafts (28 of 60 kidneys), *in situ* artery (five), a synthetic graft (six), no revascularization (ten) or nephrectomy (11) were performed.

Results: Four deaths (13 per cent; three from myocardial infarction (MI) and one from multiple organ system failure) and one graft occlusion (long-term dialysis) occurred within 30 days. Two of 26 survivors were lost to follow-up (60 and 66 months) and eight died dialysis free (four from MI, two from stroke and two from carcinomatosis; median survival 72 (range 42–110) months). At last follow-up, three of 26 patients who required dialysis before operation were dialysis free but one had commenced dialysis. Nineteen of 26 had a reduction in creatinine level of more than 15 per cent (median 129 (range 114–262) μmol l^{-1}) and six had no change. Fifteen patients had improved blood pressure control (fewer antihypertensive drugs) and 16 remained under review (follow-up 72 (range 36–130) months).

Conclusion: Long-term follow-up suggests that surgery confers a survival benefit for patients and preserves renal function. Although most patients with BRAS are now managed by interventional radiology, renal revascularization has a definite role in patients requiring aortic surgery.

Structure and biomechanics of venous tissue from patients with abdominal aortic aneurysm

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Background: Patients with abdominal aortic aneurysm (AAA) exhibit generalized arteriomegaly and abnormal proteolysis throughout the vasculature. Current evidence suggests that AAAs are a localized manifestation of a systemic disease that affects both arteries and veins. Tissue from AAAs is characterized by a loss of elastin, reduced tensile strength and increased stiffness. The aim of this study was to determine whether these changes were present in the venous tissue of patients with AAA.

Methods: A segment of inferior mesenteric vein (IMV) was harvested from patients undergoing aneurysm repair (n = 11) or left colon resection (n = 11). Matrix composition of the vessel (relative proportions of collagen, elastin and smooth muscle cells) was determined by stereology. Biomechanical properties (tensile strength, Young's modulus) were calculated by elongation of tissue using a tensile testing machine. Data are presented as median (interquartile range) and compared with the Mann–Whitney test.

Results: The medial elastin content in IMV from the AAA group was markedly reduced (19·4 (17·2–24·8) *versus* 26·8 (23·7–29·9) per cent; P = 0·018). Mechanical testing revealed a significant reduction in the tensile strength from 2·9 (2·0–4·2) MPa in controls to 1·4 (0·8–2·5) MPa in the AAA cohort (P = 0·007). This corresponded with a significant reduction in Young's modulus of elasticity in the AAA group (2·7 (2·0–3·1) *versus* 5·4 (4·2–81·0) MPa; P < 0·001).

Conclusion: Reduction in tensile strength and stiffness in venous tissue from patients with AAA was associated with disruption and reduction of the elastin content of the vein wall. These changes are analogous to those observed in the arterial aneurysm wall and confirm the systemic nature of aneurysm disease.

Systemic inflammatory response syndrome precedes multiorgan failure following abdominal aortic aneurysm repair

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Background: The systemic inflammatory response syndrome (SIRS) is defined as the first stage of a process progressing through sepsis, septic shock and multiple organ failure (MOF). The aim of this study was to determine the incidence of SIRS following abdominal aortic aneurysm (AAA) repair, its temporal relationship to the development of organ failure and whether it is a better predictor of organ failure than commonly used prognostic scoring systems.

Methods: The presence of SIRS and organ failure was recorded daily for 76 patients undergoing AAA repair over a 9-month interval (49 elective repair (EAAA), 20 ruptured AAA repair (RAAA) and seven urgent repair (UAAA)). An Acute Physiology And Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Score (SAPS) II, and Physiological and Operative Severity Score for enUmeration of Mortality and morbidity (POSSUM) score was calculated for each patient.

Results: Forty-three patients who had EAAA and all patients who had either RAAA or UAAA developed SIRS during their admission. Thirteen patients who had RAAA developed MOF, 12 of whom had SIRS before this. Seventeen of 20 patients in the elective group with one or more organ failures developed SIRS before organ failure. Two patients who had EAAA and four who had UAAA developed MOF, all of whom had SIRS before this. SAPS II scores were significantly higher in patients with RAAA who developed MOF (P = 0·03, Mann–Whitney U test).

Conclusion: MOF following AAA repair is preceded by SIRS in the majority of cases. SIRS is therefore a sensitive but non-specific indicator of impending MOF. It is better than more complex scoring systems such as APACHE II, SAPS II and POSSUM.

Cost of emergency ruptured abdominal aortic aneurysm repair

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Background: Cost analyses of elective abdominal aortic aneurysm (AAA) repair are well documented but accurate data for ruptured AAA repair are more scarce. The aim of this study was to document the costs of salvaging a series of recent patients with a ruptured AAA who survived following extensive intensive care input.

Methods: Details of AAA repairs between January 2000 and July 2001 were obtained from the vascular database. Costs were calculated based on duration of stay in the intensive therapy unit and ward, theatre sessions and use of the radiology and pathology services. The figures are valid for prices at year 2000. The cost of repair was compared between three groups: elective, uncomplicated rupture and complicated rupture. Complicated repairs were associated with one or more system failures.

Results: There were 110 aneurysms, 63 in the elective group and 47 ruptures. In the ruptured group, 27 were 'uncomplicated' and 12 were 'complicated'. No operation was performed in eight patients with a ruptured AAA and these were excluded from operative cost analysis. The mean age of the patients was 72 years and 91 per cent were men. The mortality rate for was 1·6 per cent for elective repair and 17·9 per cent for ruptured repair. The median (range) cost of repair was £4762 (2925–47 499), £7075 (2012–13 756) and £20 075 (13 864–166 446) for elective operation, uncomplicated rupture and complicated rupture respectively.

Conclusion: These results show that a relatively low mortality rate for ruptured AAA repair can be achieved but at a significant cost. Saving the £166 446 spent on the single most expensive ruptured AAA repair would cover the costs of a local aneurysm screening programme for many years.

Anatomical factors for aneurysm rupture, conversion and death after endovascular aortic aneurysm repair

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Background: Endovascular aortic aneurysm repair (EVAR) is an acceptable alternative to conventional open aneurysm repair. The aim of this study was to identify anatomical factors predisposing to conversion, aneurysm rupture and death following EVAR.

Methods: Some 3414 patients underwent EVAR from January 1994 to June 2001. Anatomical details of all aneurysms were recorded before the procedure; details of patients with and without complications of rupture, conversion and death were compared. Standard aortic diameters from D1 to D5L, standard aneurysm lengths, H1 to H4L, angulation of the aortic neck, the aneurysm itself, and iliac angulation both right and left were analysed. Data were analysed using the Mann–Whitney *U* test and life regression analysis.

Results: Conversion to open repair occurred in 139 patients, and was more frequent with greater dimensions of D1 ($P < 0{\cdot}01$), D2a ($P < 0{\cdot}01$), D2c ($P = 0{\cdot}02$), D3 ($P < 0{\cdot}01$) and shorter H1 ($P < 0{\cdot}01$). Aneurysm rupture (22 patients) correlated with the dimension of D1 ($P = 0{\cdot}02$), D2c ($P = 0{\cdot}05$), D3 ($P < 0{\cdot}01$), H2 ($P < 0{\cdot}01$), H3 ($P < 0{\cdot}01$), angulation of the aortic neck ($P = 0{\cdot}01$) and right iliac angulation ($P < 0{\cdot}01$). Aneurysm-related death (352 patients) was associated with D1 ($P < 0{\cdot}01$), D2c ($P = 0{\cdot}05$), D3 ($P < 0{\cdot}01$), H2 ($P < 0{\cdot}01$), angulation of the aortic neck ($P < 0{\cdot}01$) and right iliac angulation ($P < 0{\cdot}01$). The greatest difference in dimension was for D3: 67·1 *versus* 56·4 mm for aneurysm rupture, 58·8 *versus* 56·4 mm for conversion and 60·0 *versus* 56·1 mm for death after EVAR.

Conclusion: Larger aneurysms are more prone to conversion, aneurysm rupture and patient death following EVAR.

Outcomes after fasciotomy for compartment syndrome by vascular surgeons

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Background: Compartment syndrome should be anticipated and prevented by timely fasciotomy after revascularization for profound limb ischaemia. The objectives of the study were to analyse the time sensitivity and outcome of fasciotomy for compartment syndrome in vascular patients.

Methods: This was an analysis of prospectively collected data (1986–2001).

Results: Some 59 legs and one arm in 58 patients underwent fasciotomy. Causes of ischaemia included balloon embolectomy/thrombectomy (24), elective reconstruction (one), emergency bypass (18), angiography (three), intra-aortic balloon pump (two), aortic dissection (one), prolonged Lloyd-Davies position (three), phlegmasia cerulae dolens (one), tibial fracture (four), arm soft tissue injury (one) and unknown cause (one). There were ten deaths (17 per cent) and 15 major amputations (25 per cent). Of the remainder, 24 had no neurological deficit and good function, and 12 had a footdrop. In surviving legs, ten required skin grafting, nine needed debridement of dead muscle and there were six superficial wound infections. The incidence of death (18 *versus* 17 per cent) and limb loss (32 *versus* 25 per cent) was similar for prophylactic (28) and therapeutic (32) fasciotomies. However, the risk of footdrop was increased (28 *versus* 11 per cent) in therapeutic decompressions. The worst results were in patients presenting late to vascular surgeons. Their risk of footdrop was increased (80 *versus* 17 per cent; $P = 0·01$) owing to delay (34 *versus* 19 h) from the onset of symptoms to fasciotomy.

Conclusion: The success of fasciotomy for compartment syndrome is highly time sensitive, and poor outcomes (footdrop, muscle debridement and amputation) are associated with late recognition and delay in treatment. Raised compartment pressures should be anticipated, with a low threshold for surgical decompression.

Prospective randomized study of postoperative pain after thoracoscopic dorsal sympathectomy: harmonic scalpel *versus* conventional diathermy

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Background: Dorsal thoracoscopic sympathectomy for axillary and/or palmar hyperhidrosis results in significant postoperative pain over the anterior chest and interscapular regions. This prospective randomized study investigated the difference between conventional diathermy (high local temperatures and conducted heat injury) and the harmonic scalpel (less than 1 mm surrounding tissue damage) for nerve ablation with regard to postoperative pain (visual analogue score), requirement for opiate analgesia and quality of life at 6 weeks (Short Form (SF) 36).

Methods: Nine patients in each group all received the same balanced anaesthetic. Visual analogue pain scores were recorded at 6, 12 and 24 h after surgery, and then daily until day 14, and the total intravenous morphine requirement was measured (patient-controlled analgesia system) for 24 h after operation. The SF-36 questionnaire was completed before operation and at 6 weeks.

Results: Median pain scores were significantly reduced in the harmonic scalpel group at 6 h (25 *versus* 45; $P = 0·013$), 12 h (17 *versus* 42; $P = 0·021$) and 24 h (9 *versus* 42; $P = 0·012$) after the procedure and remained lower than those for conventional diathermy for a further 3 days. In addition, the median intravenous morphine requirement was significantly lower in the harmonic scalpel group at 24 h (32 *versus* 55 mg; $P = 0·007$). At 6 weeks all the patients reported relief of symptoms and showed significant improvements in quality of life scores. There were no intergroup differences.

Conclusion: Use of the harmonic scalpel for dorsal thoracoscopic sympathectomy results in significantly less early postoperative pain and is as effective as conventional diathermy in relieving symptoms and improving quality of life.

Inhibitory effect of aspirin on platelet aggregation is significantly reduced during carotid surgery

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Background: Despite the use of aspirin, patients undergoing carotid surgery still suffer thromboembolic complications. Stress is known to reduce the effectiveness of aspirin as an inhibitor of platelet aggregation to arachidonic acid (AA). The authors investigated whether the stress of surgery can overcome the inhibitory effect of aspirin on platelet function.

Methods: Forty patients undergoing carotid endarterectomy all received aspirin 150 mg daily. Blood samples were taken before and during operation to assess platelet aggregation and P-selectin expression in response to AA 5 mmol as measured by flow cytometry.

Results: Aggregation in response to AA increased from a mean(s.d.) of 13·4(17·4) to 54·4(30·5) per cent during surgery ($P < 0·01$). This increase was not due to release of adenosine 5′-diphosphate (ADP), thrombin or adrenaline as it was not blocked by inhibitors of ADP (apyrase 4 µg ml^{-1}), thrombin (hirudin 10 units ml^{-1}) and adrenaline (yohimbine 10 µmol). Aggregation in response to ADP 4×10^{-6} mol l^{-1} and collagen 1 µg ml^{-1} also increased significantly during surgery ($P < 0·05$), as did spontaneous aggregation, which increased from 1·1(1·2) to 4·0(3·6) per cent ($P < 0·01$). The mean(s.d.) proportion of platelets expressing P-selectin in response to AA increased from 4·9(4·0) per cent before surgery to 14·9(14·7) per cent during operation ($P = 0·05$).

Conclusion: Although aspirin irreversibly inhibits the cyclooxygenase pathway, blocking platelet aggregation in response to AA, this effect is negated during carotid surgery. While accompanied by increased platelet degranulation (as evidenced by increased P-selectin expression), this effect was not due to increased release of ADP, thrombin or adrenaline. The ability of platelets to escape from cyclooxygenase inhibition may play a central role in postintervention thrombosis.

Disease progression following endoluminal bypass for femoropopliteal disease

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Background: While the early results for endoluminal grafts (ELGs) within the femoropopliteal segment have been promising, there is a paucity of mid- and long-term data. The aim was therefore to evaluate clinical and angiographic outcomes 4 years following ELG deployment into the femoropopliteal segment.

Methods: All patients ($n = 22$) who had an ELG deployed for either occlusive or stenotic disease were followed for a minimum of 4 years with measurement of ankle : brachial pressure indices, duplex imaging and angiography. A comparison was made of the proximal and distal vessel appearances both at the time of ELG deployment and at subsequent angiography.

Results: Primary and secondary patency rates at 4 years were 44 and 64 per cent respectively; all ELG failures ($n = 8$) occurred within 6 months of deployment. While there was no significant deterioration in symptoms in limbs with a patent ELG ($n = 14$) at 4 years, there was significant distal disease progression in five patients as well as neointimal hyperplasia within the anchoring stents in seven ELGs.

Conclusion: Although continued ELG developments may reduce the incidence of early graft failures, neointimal hyperplasia and distal disease progression are two factors that must be addressed in order to maintain long-term graft patency.

Audit of out-of-hours interventional vascular radiology

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Background: In 1996 the Royal College of Radiologists established a set of guidelines for out-of-hours radiology. The authors audited unit activity in the light of these guidelines and also the perceived increase in out-of-hours district general hospital referrals.

Methods: This was a retrospective study that examined the number of emergency vascular radiology requests booked over 1 year (October 1999 to October 2000). Patients were identified from the vascular radiology database and case notes were reviewed.

Results: A total of 1902 patients had angiography, with 686 having further procedures. Only 17 patients (0·9 per cent) were actually investigated out of hours. Five of 17 patients received thrombolysis and seven had either an angioplasty or stent. Despite being a tertiary referral centre only two patients were extrahospital referrals. The time spent performing procedures was 66 h. Overall, nearly 70 per cent of patients had an intervention performed within the first 24 h, and only one had angiography alone. The 30-day limb salvage rate was 88 per cent (15 of 17) and there were two below-knee amputations. The overall 30-day patient survival rate was 88 per cent; two patients died from myocardial infarction.

Conclusion: Only a small number of patients actually required emergency angiography, despite large numbers booked. This is probably as a result of a good in-hours service. Extrahospital referrals need not generate large amounts of out-of-hours work. A case can be made for centralization of emergency out-of-hours vascular radiology and subsequent aftercare. Of the 17 patients requiring the service, most had urgent intervention indicating appropriate service use.

Assessment and monitoring of patients with intermittent claudication

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Background: Traditional use of treadmill walking and ankle : brachial pressure indices (ABPIs) in evaluating patients with intermittent claudication may not adequately address the disease impact on patients' quality of life. If new measures such as disease-specific quality of life questionnaires (DSQs) and the 6-min walking test (SMW) are to be considered, they should be shown to have greater reliability and improve upon these established tests.

Methods: Thirty-seven patients (median age 68 (range 50–85) years) with confirmed peripheral arterial disease were recruited. Each patient was assessed by the validated DSQ, ABPIs, constant load treadmill test (CLT) at 3·5 km and 12 per cent gradient to absolute claudication time (ACT), and the SMW. The CLT and SMW test were repeated 1 week later to assess reproducibility.

Results: All patients were able to perform the SMW (mean 392 m) and complete the DSQ. The SMW variability was 5 (95 per cent confidence inteval (c.i.) −9 to 17) per cent. Thirty-three patients were able to perform the CLT to ACT (mean 127 s); the variability was 24 (95 per cent c.i. −63 to 66) per cent. Spearman correlation was greatest between the DSQ and the SMW ($\rho = 0{\cdot}57, P < 0{\cdot}001$). Other significant correlations were SMW with CLT ($\rho = 0{\cdot}46$, $P = 0{\cdot}007$), DSQ with CLT ($\rho = 0{\cdot}36$, $P = 0{\cdot}038$) and SMW with ABPI ($\rho = 0{\cdot}32$, $P = 0{\cdot}048$).

Conclusion: The SMW was easier for patients to perform, more reproducible than the CLT and correlated with the DSQ, CLT and ABPI. The strong correlation between the SMW and the DSQ means that use of the questionnaire alone may be sufficient for assessing and monitoring claudicants.

Outcomes of a clinic for the management of intermittent claudication

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Background: This study reports the effects of a claudication clinic, incorporating home-based and gym-based exercise programmes, on maximum walking distance (MWD) and speed, and in identifying vascular risk factors.

Methods: Over 29 months to June 2001, 97 patients were assessed in a claudication clinic by a nurse specialist. MWD and walking speed were measured using a corridor walking test at each patient's pace. A home-based exercise programme and vascular risk factors were discussed. Patients were invited to attend exercise classes run by the nurse and a physiotherapist. MWD and speed were reassessed at 1, 3, 6 and 12 months.

Results: Thirty patients on a gym-based programme and 33 on a home-based programme completed at least

3 months' follow-up. Median MWD increased from 362 to 562 m at 3 months for the gym-based group ($P < 0{\cdot}01$, Wilcoxon signed rank test), and from 300 to 342 m for the 'home' group ($P < 0{\cdot}01$). Median walking speed increased from 4·11 to 4·48 km h^{-1} ($P < 0{\cdot}01$) for the 'gym' group, and from 3·88 to 3·96 km h^{-1} ($P = 0{\cdot}04$) for 'home' group. Risk factor modification advice, additional to that already given by the vascular surgeons, was required by 86 per cent of patients, including advice on hyperlipidaemia (40 per cent), current/recent smoking (34 per cent), diabetes mellitus (26 per cent), diet (15 per cent), hypertension (8 per cent), antiplatelet medication (5 per cent) and alcohol (3 per cent).

Conclusion: The use of a corridor walking test enabled the demonstration of significantly increased speed and MWD after home-based and gym-based claudication exercise programmes, with greater benefits in the latter patients. A nurse-led claudication clinic was an effective means of facilitating the exercise programmes and of identifying previously unaddressed risk factors.

Potential role of endothelin 1 in ischaemia-induced angiogenesis in critical limb ischaemia

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Background: The vasoconstrictor peptide endothelin (ET) 1 has mitogenic properties on endothelial cells and promotes angiogenesis in tumour models. Angiogenesis occurs in ischaemic skeletal muscle and, since raised circulating levels of ET-1 are found in patients with critical leg ischaemia (CLI), ET-1 may be involved in ischaemia-induced angiogenesis in human skeletal muscle. In this study, microvessels in critically ischaemic muscle were quantified and their relationship to the distribution of ET receptors was studied.

Methods: Open muscle biopsies were obtained from the leg of 12 patients with CLI, and from 12 patients without leg ischaemia. Microvessels were identified on muscle sections using immunomarkers (CD31 for endothelial cells; anti-smooth muscle α-actin for vascular smooth muscle cells) and quantified by counting the number of immunopositive cells per unit area at × 200 magnification. ETA and ETB receptor binding was localized and assessed by *in vitro* autoradiography, and receptor messenger RNA expression was studied using real-time reverse transcriptase–polymerase chain reaction.

Results: CD31 and antismooth muscle α-actin immunostaining co-localized, confirming the identity of microvessels. The number of microvessels in CLI biopsies was 2·5 times higher than that in controls ($P < 0{\cdot}01$, Mann–Whitney *U* test). ETB receptor gene expression and ETB receptor binding were significantly increased in CLI ($P < 0{\cdot}01$). ETA receptor binding was increased, but this did not reach significance. High-resolution autoradiography confirmed that binding was associated with microvessels.

Conclusion: These results show that angiogenesis occurs in chronically ischaemic muscle in humans. A raised level of ETB receptors within the muscle is associated with newly formed microvessels, suggesting that ET-1 may mediate angiogenesis via these receptors and improve muscle perfusion during ischaemia.

Patient-determined quality of life measure in critical limb ischaemia

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Background: The aim of this study was to evaluate whether a patient-generated quality of life measure, the Schedule for the Evaluation of Individual Quality of Life (SEIQoL-dw), provides a different insight into the impact of intervention for critical limb ischaemia on the changes in quality of life experienced by patients.

Methods: Consecutive patients admitted into a single centre with critical limb ischaemia were assessed for inclusion in this prospective study. Patients completed the Medical Outcomes Short Form (SF) 36 and EuroQol questionnaires, and were interviewed by a single clinician to complete the SEIQoL-dw. Those who underwent surgical revascularization or amputation were re-evaluated 6 months after operation.

Results: One hundred and twelve patients completed all assessments before management of their critical limb ischaemia. At 6 months not all were willing and the mortality rate was 38 per cent; 41 patients completed follow-up assessments. Of these 31 had a patent graft, eight a below-knee amputation and two an above-knee amputation. Unsuccessful bypass grafts had preceded one above- and two below-knee amputations. The median (range) preoperative SEIQoL-dw score for those undergoing amputation was 59·9 (34·8–95·4), while for those with a bypass graft it was 52·2 (7·0–86·6). Corresponding post-operative scores were 73·3 (25·8–100) and 60·1 (17·8–89·1). All but one patient with an amputation determined their quality of life to have improved, compared with 20 of those with a patent graft.

Conclusion: Amputation can be associated with a significant improvement in quality of life when this is measured according to an individual's priorities.

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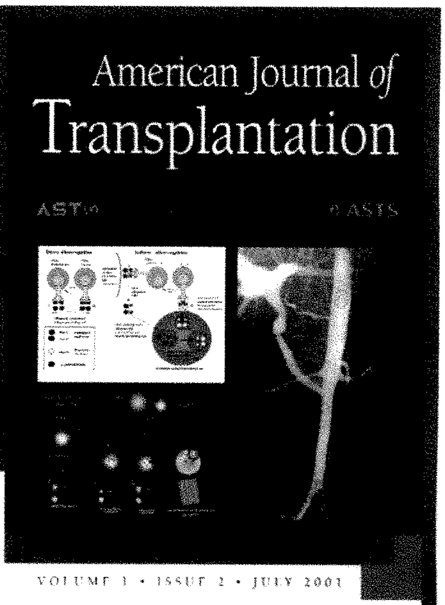
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